SMOKELESS TOBACCO: CURRENT USE AMONG BANGLADESHI ADOLESCENTS AND ASSOCIATION WITH INCREASED ORAL CANCER RISK AMONG BANGLADESHI ADULTS

By

MD ZAHID ULLAH

BDS MPH MBA

A thesis submitted in partial fulfilment of the

requirements of the University of Wolverhampton

for the degree of Doctor of Philosophy

June 2020

This work or any part thereof has not previously been presented in any form to the University or to any other body whether for the purposes of assessment, publication or for any other purpose (unless otherwise indicated). Save for any express acknowledgements, references and/or bibliographies cited in the work, I confirm that the intellectual content of the work is the result of my own efforts and of no other person.

Signature……………………………………….

Date 26/06/2020

Abstract

Background: Smokeless tobacco (SLT) use is a major public health burden and highly prevalent in Bangladesh. Over 20 million Bangladeshi adults are currently using SLT. Bangladesh Government had announced its vision to become a tobacco free country by 2040. Therefore, public health efforts focusing on preventing SLT onset among adolescents would contribute towards this vision. However, apart from national adolescent SLT prevalence from Global youth Tobacco Survey (GYTS), no other information linked to adolescent SLT use is available to inform future interventions. Also, SLT use related health burden such as oral cancer is highly prevalent in Bangladesh. Globally, Bangladesh ranked third for oral cancer related death. Every year over 8,000 Bangladeshi adults lost their lives because of this deadly disease. Regarding the relationship between SLT and oral cancer risk, there is a disconnection between the study findings from the western countries and developing countries. With the diversity of SLT products and its content there is a need to produce local evidence. Therefore, the overall aim of this PhD research was to examine the factors contributing to adolescent SLT use in Bangladesh and the role of SLT in oral carcinogenesis among Bangladeshi adults.

Methods: To attain the study objectives, in 2015 a cross-sectional survey (n=790, response rate 100%) in two rural secondary schools and a hospital-based case-control study (n=507; case:169 and controls: 338, case participation rate 92.86%) were carried out in Bangladesh.

Results: The findings of the adolescent cross-sectional survey suggest that the ever and current SLT prevalence among rural Bangladeshi adolescent was 9.5% (75) and 3.7% (29) respectively. Males were the leading users of SLT. Zarda (80%) is the most common type of SLT used by the adolescents. Rural Bangladeshi adolescent started using SLT as early as seven years old and younger. Social sources (41.4%) were the most common source of SLT reported. Most adolescents (65.2%) were able to buy SLT from commercial stores without any restrictions. Many current SLT users (89.7%) wanted to quit SLT but professional help was not available. Overall, adolescents had good knowledge about the adverse effects of SLT use, though misconceptions about the addictive nature of SLT use were prevalent. Older age, self-efficacy, perceived barriers, perceived benefits and perceived severity were the significant predictors of adolescent SLT use.

The findings of the hospital-based case-control study suggest a strong association between SLT use and oral cancer risk among Bangladeshi adults. Women [OR: 14.33 (95%CI: 6.33-32.42)] had the higher risk of developing oral cancer than men [OR: 5.29 (95%CI: 2.62-10.67)] from SLT use. Among men highest risk was observed among dual users (SLT and smoking) [OR: 17.23 (95%CI: 5.70-52.01)]. Both Betel Quid (BQ) with and without tobacco increased the oral cancer risk. However, the risk was lower for chewing BQ without tobacco than BQ with tobacco. The risk of oral cancer increased with the increasing frequency and intensity of SLT use. About 61% of all oral cancer cases in Bangladesh were attributable to SLT use. Among other oral cancer risk factors - bidi

smoking, oral hygiene factors and leanness were associated with increased oral cancer risk.

Conclusion: The findings of the present cross-sectional survey and hospital-based case-control study were comparable to existing literatures. Our evidence suggests that SLT use among rural Bangladeshi adolescent is low compared to other neighbouring countries. However, initiation of SLT at an early age is a public health concern. Lack of professional help to quit SLT and poor implementation of tobacco control laws were prevalent. Overall knowledge about SLT use and its ill effects was good, but misconceptions were prevalent. The case-control study demonstrated a significant increase of risk of oral cancer is associated with SLT use. Women had higher risk of developing oral cancer of SLT use than men. For men dual use of SLT and smoking was the major risk factor. Both BQ with and without tobacco was associated with oral cancer incidence. A large number of oral cancer cases in Bangladesh is preventable by tackling the SLT epidemic.

TABLE OF CONTENTS

List of Tables

List of figures

List of abbreviations

AC	Attributable incidence cases
AIC	Akaike information criterion
ASR	Age-standardised rate
AUC	Area under curve
BMI	Body mass index
CDC	Centers for disease control and prevention
CI	Confidence Interval
DALY	Disability-adjusted life years
EC	Environmental Council
FCTC	Framework Convention on Tobacco Control
GATS	Global Adult Tobacco Survey
GDP	Gross domestic product
GYTS	Global Youth Tobacco Survey
HBM	Health belief model
HNC	Head and neck cancer
HPV	Human papilloma virus
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
INHANCE	International Head and Neck Cancer Epidemiology
ITC	International Tobacco Control
KSA	Kingdom of Saudi Arabia
LIC	Lower-income countries
LMIC	Lower-middle-income countries
MDG	Millennium Development Goals
MDS	Mediterranean diet score
MOHFW	Ministry of Health and Family Welfare

NCD	Non-communicable diseases
NCI	National Cancer Institute
NGO	Non-governmental organisations
NNK	Nicotine-derived nitrosamine ketone
OR	Odds ratio
PAF	Population attributable fraction
PAR	Population attributable risk
PATH	Population Assessment of Tobacco and Health study
RA	Research assistants
RR	Relative risk
SCT	Social cognitive theory
SDG	Sustainable development goals
SEAR	South-East Asia Region
SES	Socio-economic status
SLT	Smokeless tobacco
ST	Smoked Tobacco
TCA	Tobacco Control Act
TNM	Tumour Nodes Metastasis
UADT	Upper aerodigestive tract
UMIC	Upper-middle-income countries
VAT	Value added tax
WHO	World Health Organisation

Preface

While growing up in a culture where Smokeless tobacco (SLT) use is mostly deemed as a shared social activity performed with friends and family members that has been incorporated into social activities and social rituals, such as festivals and weddings, I always felt that trying SLT occasionally would not do any harm, since the use of SLT has passed from generation to generation as a family and cultural tradition. However, my observation started changing when I started studying in one of the country's most renowned public dental college.

During my placement in the final year and internship, I started noticing that many oral cancer patients visited the oral surgery outpatient department, and there was one thing that most of the patients, if not all, had in common – they were SLT users. There is a high prevalence of SLT use in Bangladesh, one of the highest in the world, and the burden related to it is substantial. Bangladesh has also got the second highest number of oral cancer-related deaths in the world.

I always aspired to do something about this national crisis through public health efforts. While my colleagues were committed to their clinical career, I always wanted to be a public health professional, as I am a strong believer that prevention is better than cure. To follow my dream, I achieved an MSc in Public Health and MBA in hospital and health services management from UK universities and I am now working as a Senior Public Health Officer for one of the local authorities in the United Kingdom (the UK).

While looking at the evidence of oral cancer being associated with SLT use, I found there was not a single study from Bangladesh that investigated this association. Then in 2014, a global report on Smokeless tobacco was published by the National Cancer Institute Centers for Disease Control and Prevention U.S. Department of Health and Human Services, titled "Smokeless Tobacco and Public Health: A Global Perspective." The report was a real eye-opener and emphasised the importance of yielding local evidence.

Appreciating the importance of generating local evidence, this PhD research has looked at this relationship between SLT use and oral cancer risk in the Bangladeshi context. However, I did not only want to focus on the problem but also to explore a possible solution to it. Therefore, this PhD research also looked at the determinants of adolescent SLT use in Bangladesh. Exploring the key factors of adolescent SLT use was sought to inform communication, educational, and regulatory strategies that are aimed at reducing SLT onset among the most vulnerable group.

We know research is generally understood to be a systematic process to generate new knowledge and can act as a powerful tool for providing information for policy formation. It is envisaged that the findings of this PhD research will produce evidence of SLT-related harm in Bangladesh. Those appropriate policies can be formulated in order to eliminate this national burden. Also, identifying the key factors of adolescent SLT use may help in the aid intervention programmes in the adolescent population in Bangladesh, as preventing SLT onset among adolescents would hugely contribute towards the Bangladesh Governments' vision to become a tobacco-free country by 2040.

Acknowledgement

I wish to express my sincere gratitude and appreciation to my PhD supervisor Dr Jennifer NW Lim for being just more than a supervisor and guide me during the past years. She always takes a great interest in my work and offered me wholehearted support and encouragement to get the best out of me. I am forever indebted for her guidance, advice, and encouragement. Without her support, I could never complete this PhD project. She was always there when I needed her help. She was a true mentor one can wish for. I also want to extend my heartfelt gratefulness to my Co-supervisor Dr Marc Chrysanthou for assisting and supporting me for the past year. A special thanks to Prof Bas Bueno-de-Mesquita, visiting professor, Dept. of Epidemiology and Biostatics, Imperial College London for his guidance and suggestions for the hospital-based case-control study. His useful advice and feedback helped me to conduct the case-control study efficaciously.

I want to express gratitude to my thesis examiners Professor Kamran Siddiqi and Professor Rebecca Jester for their valuable comments. I am extremely thankful to my previous supervisory team in Anglia Ruskin University, Dr Marie-Ann Ha, Dr Nebil Achour, Jufen Zhang, who gave me advice and support to complete this work.

I am also indebted to Dr Md Sadat Hosen Shahriar and Dr Ashis Dhar for assisting during field data collection in the hospital. Without their help, I could not complete 507 interviews in six months. I also want to thank all the clinicians in the participating hospital for supporting me during data collection.

My words are not enough to express my gratitude to all the study participants for the case-control study and their friends and families. Despite their grief and difficulties, they showed their support for the present study. It would be impossible to complete this study without their immense contribution. I am very thankful to the all the students that took part in cross-sectional survey. A special thanks to the head teachers and parents for their support and consent.

My family deserves a special thanks for their constant support, love and care throughout my academic life. I want to thank my father Dr Md Hafiz Ullah for his support and encouragement, who always believed in me, who encouraged me to dream big. My mother, Mrs Lutfun Nahar always encouraged me to achieve my goals. My wife Mrs Faria Akther, my Son Wafiq Ayan, my daughter Wania Ayra showed incredible love, care and patience during this time. My brother Md Saif Ullah, my sister Nishar Z Islam for constantly supporting me in achieving my dream.

Published article and conference abstract

Ullah, M.Z., Lim, J.N., Ha, M. and Rahman, M.M. (2018) 'Smokeless tobacco use: pattern of use, knowledge and perceptions among rural Bangladeshi adolescents', *PeerJ,* 6, pp. e5463. doi: 10.7717/peerj.5463. (see Appendix A for full text)

Ullah, M.Z., Lim, J.N., Ha, M. and Bueno-de-Mesquita, B. (2018) 'Predictors of patient-related delay of oral cancer diagnosis in Bangladesh', *European Journal of Surgical Oncology,* 44, pp. S50. doi: 10.1016/j.ejso.2018.01.019. (see Appendix A for full abstract)

Chapter I. Introduction

1.1 Smokeless tobacco

According to the Centres for Disease Control and Prevention (CDC, 2018), SLT refers to tobacco that is not burnt but chewed, spit or swallowed and contains nicotine, which is highly addictive. Unlike smoked tobacco that is burnt and then inhaled, such as cigarettes, cigars or water pipes, SLT is used orally or nasally, which results in the absorption of nicotine and other harmful chemicals through mucous membranes (Bofetta *et al.,* 2008).

The practice of SLT use dates back to as early as the 1400s. Native Americans were probably the first people to have chewed tobacco (IARC, 2007), and they believed SLT had several medicinal uses, including easing toothache, disinfecting cuts with tobacco juice and relieving the effects of insects and snake bites (Axton, 2015). In the early 17th century, tobacco became a major export of the American colonies and various forms of tobacco use spread across Europe, Russia, China and other parts of the world (Christen *et al.*, 1982).

In the 1600s, tobacco was introduced into South Asia as a product to smoke, and since then, tobacco has been used in different forms (Gupta and Ray, 2003). Betel quid (BQ) chewing (a type of SLT commonly used in South-East Asia) was a popular practice that has existed for over 2,000 years, and after its introduction, tobacco became a popular ingredient in BQ. Later, BQ with tobacco became the most used form of SLT in South-Asia (Gupta and Ray, 2003). Today, over 300 million people from 70 low-, medium- and high-income countries use SLT (NCI and CDC, 2014).

1.1.1 Types of smokeless tobacco used across regions

Based on its mode of use, the IARC has categorised SLT into two main groups: oral use and nasal use. Oral use of SLT products is further split into three categories: sucking, chewing and other oral uses (IARC, 2007). Table 1 shows the type of SLT, according to its use.

Table 1: Type of smokeless tobacco, according to the mode of use

Oral use			**Nasal use**
Sucking	**Chewing**	**Other oral uses**	
Chimo	Betel quid	Creamy stuff	Dry snuff
Dry snuff	Gutka	Gudhaku	Liquid snuff
Gutka	Iq'mik	Gul	
Khaini	Khaini	Mishri	
Loose leaf	Khiwam	Red tooth powder	
Maras	Loose leaf	Tuibur	
Mishri	Mawa		
Mosit snuff	Plug		
Naswar	Tobacco chewing		
Plug	Gum		
Shammah	Twist or roll		
Toombak	Zarda		

(Source: IARC, 2007, p. 47)

Based on the production and preparation method, SLT can be further categorised into two main groups: pre-made SLT products and custom-made SLT products. There are two types of pre-made SLT products: commercial products (made in traditional manufacturing settings) and cottage products (made in a non-traditional environment, such as shops, houses, market halls and street vendors, and sold in non-commercial packaging, e.g. wrapped in paper or plastic bags) (NCI and CDC, 2014). Table 2 shows a list of SLT products, based on their manufacture and preparation.

Table 2: Characteristics and examples of pre-made and custom-made smokeless tobacco products

Premade manufactured	Premade cottage industry	Custom-made vendor/individual
• Made in advance for sale • Made in a manufacturing environment • Sealed in labeled commercial packaging	• Made in advance for sale • Usually handmade in non-traditional environments • Often sold in non-commercial packaging	• Made by a vendor or individual according to user preferences, generally for immediate consumption • Involves mixing two or more components (including premade products) together by hand to form a final product
Product examples: • Chewing tobacco (plug/twist/loose leaf) • Creamy snuff • Dissolvables • Dry snuff • Gudahku/Gudahka • Gutka • Khaini • Moist snuff • Kiwam • Rapé • Red toothpowder	Product examples: • Dohra • Gutka • Mainpuri • Nass/Naswar • Nasway • Betel quid with tobacco (paan) • Rapé • Shammah • Toombak • Tuibur	Product examples: • Gudahku/Gudahka • Iqmik • Nass/Naswar • Nasway • Betel quid with tobacco (paan) • Rapé • Shammah • Tapkeer • Tobacco leaf • Tombol • Toombak Some premade ingredients are used to make custom-made products: twist, zarda, toombak, gudahku/gudahka, and kiwam.

(Source: NCI and CDC, 2014, p. 81.)

Globally, SLT products are used in different forms and their contents vary extensively across regions. Table 3 below lists the types of SLT products used in WHO regions.

Table 3: Types and names of smokeless tobacco used in WHO regions

SLT product	WHO region					
	AFRO	AMRO	EMRO	EURO	SEARO	WPRO
Oral use						
BQ With Tobacco			X		X	X
Chimo		X				
Creamy Snuff					X	
Dry Snuff	X	X		X		
Gul					X	
Gudhaku					X	
Gutka					X	
Iq'mik		X				
Khaini					X	
Khiwam					X	
Loose Leaf		X		X		
Maras				X		
Mawa					X	
Mishri					X	
Mosit Snuff		X	X			
Naswar	X		X	X	X	
Plug		X				
Red Tooth Powder					X	
Shammah			X	X		
Toomkbak	X					
Tuibur				X		
Twist						
Zarda			X		X	
Nasal use						
Dry Snuff	X		X	X	X	
Liquid Snuff	X					

(Source: IARC, 2007, p. 48)

South-East Asia

The SEAR is home to 90% of SLT users, with over 250 million SLT users living in this region (Sinha *et al.*, 2012). Oral use of SLT is widely prevalent in this region, and sun- or air-dried SLT products are used in their processed, unprocessed or manufactured forms. The most popular form of SLT in India and Bangladesh is BQ, which refers to a combination of betel leaf, areca nut and slaked lime (Sinha *et al.*, 2012).

Figure 1: Examples of smokeless tobacco products used around the world (Source: NCI and CDC, 2014, p. 80).

Using unprocessed SLT products is widely seen in various parts of India. ***Kaddipuddi*** is a cheap quality of 'tobacco powdered stick' used in Karnataka, India. ***Gundi,*** which is also known as ***kadapan,*** is made from coarsely powdered tobacco, coriander seeds and other spices. It is commonly used in Gujrat and West Bengal. ***Kiwam*** is a kind of tobacco paste that is mixed with other spices and used in North India and Pakistan. ***Zarda*** is one of the most popular SLT products in Bangladesh and India. It is generally flavoured with cardamom and chewed with BQ. Another prevalent form of SLT used in India and Bangladesh is ***gutkha***, where the dried powder form of tobacco is used to clean teeth. Powdered tobaccos are locally known as ***mishri, bajjar and gul*** and are often made at home by roasting and grinding tobacco leaves. Women from rural localities are the prime users of tobacco powders (Gupta and Ray, 2003). In Pakistan, ***naswar*** is the most frequently used SLT product. It is produced from powdered tobacco, flavoured cardamom and menthol (Bile *et al.,* 2010). ***Nass*** is another mixture of SLT powder blended with sesame oil and lime and is usually used in Central Asia, Pakistan and Iran. In Sri Lanka, tobacco with BQ is the most popular form of SLT (Somatunga *et al.,* 2012). Additional SLT products used in Sri Lanka are ***pan masala, mawa*** and ***khaini*** (tobacco blended with honey/alcohol).

North and South America

Despite a significant reduction in cigarette smoking rates among US adults, the use of other tobacco products, such as cigars and SLT, did not change over the past five decades (Agaku *et al.,* 2014). Rather, SLT prevalence increased considerably from 2002-2012 (Agaku and Alpert, 2016). Two major types of SLT are used in the US: chewing tobacco (in the form of loose leaf, plug and twist) and snuff (including **snus**), which is grounded tobacco placed between the lips or inside the cheek (NCI and CDC, 2014). The types of tobacco used vary across different regions in the United States. In North America, chewing tobacco, snuff, dry and moist are commonly used, whereas in South America, people use chimo (NCI and CDC, 2014). The chewing tobacco used by Americans overall is classified as loose leaf, plug-moist, plug-chew, twist or roll.

Europe

In Europe, SLT is popular among Swedish people despite it being the only country in Europe to achieve the WHO’s goal of having a smoking prevalence of less than 20% daily cigarettes among adults by 2000 (Furberg *et al.,* 2006). Although the prevalence of smoking in Sweden has declined over time, tobacco consumption has remained relatively stable today due to the increasing popularity of SLT. In Sweden and Norway, snus is the most popular form of SLT product. Snus is ground tobacco characterised by a lower concentration of harmful chemicals than other tobacco products but with a high concentration of nicotine. In the United Kingdom, SLT products are mostly consumed by the South-Asian community (Longman *et al.*, 2010), with the most popular being gutkha (made from tobacco powder, slaked lime, areca nut, saffron and a flavouring agent). Zarda with BQ and ***khaini*** (made from tobacco, slaked lime, indigo, cardamom and menthol) are mostly consumed by the Pakistani community (NCI and CDC, 2014).

1.1.2 Biochemical composition of smokeless tobacco

SLT products contain roughly 4,000 types of chemicals, including carcinogens, nicotine and other toxicants, that play a critical role in causing adverse health effects (Rodgman and Perfetti, 2016). Based on the available data, the IARC identified SLT as group I carcinogens to humans (IARC, 2007). To date, 28 carcinogens have been identified in SLT products. The most abundant group of carcinogens in SLT products are TSNAs and N–nitrosoamino acids (Hoffmann and Djordjevic, 1997). TSNAs are considered to be the most potent because of their level of carcinogenicity and concentration in SLT (XUE *et al.*, 2014). Nicotine-derived nitrosamine ketone (NNK) and N-nitrosonornicotine (NNN) are the two main carcinogenic compounds of TSNAs and are believed to be involved in causing oral cancer among SLT users. Other carcinogens present in the SLT products are N–nitrosoamino acids, volatile N-nitrosamines, PAHs, volatile aldehydes, inorganic compounds, metals and metalloids (Hoffmann and Djordjevic, 1997).

SLT products also contain nicotine that causes both tobacco addiction and the persistent use of SLT products. Therefore, users are continuously exposed to carcinogenic agents and toxic chemicals that cause adverse health effects (NCI and CDC, 2014). Two types of nicotine in SLT products have been identified, one is free nicotine (un-ionised nicotine) and the other is bound nicotine (ionised nicotine). One of the significant properties of free nicotine is that it can cross the cell membranes rapidly compared to bound nicotine. The amount of free nicotine present in SLT products depends on the pH of the products. A higher pH SLT product has a greater proportion of free nicotine (Richter and Spierto, 2003). Unprocessed tobacco products are slightly acidic and thus contain less than 5% free nicotine. However, during SLT production, various alkaline agents are added to boost pH levels and deliver a higher amount of free nicotine to the users, which causes greater addiction.

As discussed, the content of SLT products varies substantially around the globe, as does the toxicity and carcinogenicity. An analysis of conventional moist snuff (a type of SLT product) and low-TSNAs moist snuff from the United States, Sweden and South Africa showed that mean nicotine levels in low-TSNA moist snuff products (M = 18.77 mg/g, SD = 4.89) were significantly lower than conventional products (M = 24.48 mg/g, SD = 3.39; (Song *et al.,* 2016). Among the carcinogens, conventional moist snuff had a higher level of NNK and NNN compared to low-TSNA moist snuff products. However, low-TSNA moist snuff products had a higher level of arsenic. Another study from the United States found that free nicotine in SLT products varied 350-fold and ranged from 0.01 to

3.7 mg/g. Product pH ranged from 4.7 to 7.9 and TSNA concentration ranged from 313 to 76,500 ng/g (Lawler *et al.*, 2013).

A recent analysis of SLT products from South-Asia by Stanfill *et al.,* (2018) revealed the chemical contents of several SLT products from Bangladesh. The study analysed the chemical composition of three commonly used SLT products from Bangladesh: guthka, zarda and khaini. Among all the products, two of the khaini brands had the highest pH, free nicotine and TSNA levels. Specifically, raja chap khaini had the highest free nicotine (11.9 mg/g), whereas Chaini khaini had the highest concentration of TSNAs (48.1 µg/g, wet). All zarda products had a very high concentration of nicotine (21.9–32.9 mg/g). All the guthka products contained areca nut, which is neuroactive, carcinogenic and toxic. Hossain, Hassi and Imamul Huq (2018) found that the majority of the SLT products in Bangladesh had a high concentration of heavy metals (lead, cadmium and chromium), and their potential cancer risk exceeded the acceptable limit value of 10E-4 to 10E-6. Thus, these tobacco products carry an 'unacceptable' cancer risk for the human body.

1.1.3 Oral diseases associated with smokeless tobacco use

The oral health risk associated with SLT use can differ substantially by the type of SLT, the way it is consumed and its interaction with behavioural habits, such as drinking alcohol and cigarette smoking (NCI and CDC, 2014). Demonstrating the oral effects of SLT use is complicated because of the variety of SLT products that are used around the globe, its chemical composition and the different ways they are being consumed. Therefore, the conclusion about the product characteristics and its effect on oral health may not be transferable from one country to another.

1.1.3.1 Oral mucosal lesions

Oral mucosal lesions are common in SLT users and may develop even with limited use. Pre-cancerous lesions are important as they may later turn into oral cancer, especially from leukoplakia and oral submucous fibrosis (IARC, 2004; Lee *et al.,* 2011). These types of lesions occur at the site of the SLT application and are strongly associated with the type and duration of SLT use. In a previous study from India, researchers found that pre-cancerous lesions were present among 40% of tobacco users and a longer duration of use was one of the predictive factors (Panwar *et al.*, 2012). Several studies from the Middle East, Africa, America, Europe and Scandinavian countries established that SLT clearly increases the risk of oral mucosal lesions, namely leukoplakia, erythroplakia and epithelial dysplasia. However, it is hard to quantify the risk in South Asia because of the diversity of SLT products and its compositions (IARC, 2007; Kallischnigg *et al.*, 2008; Bofetta *et al.*, 2008; Greene *et al.*, 2011; Agbor *et al.*, 2013; Al-Agili and Park, 2013).

1.1.3.2 Oral cancer

Evidence from multiple epidemiologic studies suggests a causal relationship between SLT use and oral cancer (IARC, 2007; Boffetta *et al.* 2008; Lee and Hamling, 2009). However, the risk of getting oral cancer varies substantially due to product characteristics, dosages and the duration of the use (IARC, 2007). Therefore, the risk of developing oral cancer from SLT use remains debatable. Janbaz *et al.* (2014) indicated that the risk of developing oral cancer from SLT use varied from low to medium or high depending on the balance between cancer-causing and cancer-inhibiting agents. In contrast, Swedish studies did not support the causal relationship between SLT use and oral cancer development, namely snus use and oral cancer. An extensive follow-up study among 125,576 non-smoking Swedish men confirmed no excess risk of oral cancer in snus users, but they did find snus use was independently associated with pancreatic cancer (Luo *et al.,* 2007).

1.1.3.3 Periodontal diseases

Gingival recession, especially at the site of SLT placement, is reported to be the most common periodontal changes associated with SLT use (Wenitrub and Burt, 1987; Monten *et al.,* 2006; Kumar *et al.*, 2012). SLT use is also strongly associated with severe periodontal diseases (Fisher *et al.,* 2005). A previous study from South Asia indicated that SLT use may be associated with increased periodontal destruction and tooth attachment loss (Sumanh *et al.,* 2008). A recent study from Bangladesh revealed that BQ chewing leads to poorer periodontal health (Akther *et al.,* 2008). Disagreement on this also exists, as several studies have reported no association between SLT use and gingival recession, tooth loss or bone loss (Bergstorm *et al.*, 2006; Hugoson and Rolandsson, 2011). Poor periodontal health associated with SLT use is namely supported by studies conducted in the Indian subcontinent (Parmar *et al.,* 2008; Anand *et al.,* 2013; Mohamed and Jankiram, 2013). It is possible the variance of study results is down to the different composition of SLT products used in different regions.

1.1.3.4 Dental caries

The high proportion of sugar in chewing tobacco has always been a cause of concern. The third national health survey in the United States conducted from 1988 to 1994 revealed that SLT users had a slightly higher mean number of decayed or filled teeth (Winn, 2001). However, dental caries is a multifactorial disease and, therefore, SLT use may be a co-variable in this complex process rather than a direct aetiological factor. Some studies have supported the association between dental caries and SLT use (Greer,2011; Holmen *et al.*, 2013), whereas several Swedish studies found that Swedish snus is not related to dental caries (Hugoson *et al.,* 2012; Hellqvist *et al.*, 2015). In the Indian subcontinent, studies had reported a higher association between SLT use and dental caries (Chaitanya *et al.,* 2018; Sharma, Mishra and Mittal, 2018). The difference in study findings is possibly linked to different levels of sugar in different SLT products.

1.1.4 Global smokeless tobacco prevalence and trends

According to recent WHO estimates, there are at least 367 million SLT users aged 15 years old or more worldwide (WHO, 2018a), with more male (237 million) than female (126 million) SLT users. A disproportionate number of people from lower-income areas use SLT products. More than 90% of global SLT users reside in lower-income countries (LICs) and LMICs (Sinha *et al.*, 2018). Globally, 88.5% of adult SLT users live in the following 11 countries: India (237.4 million, 66.6%), Bangladesh (30.5 million, 8.5%), Myanmar (12.6 million, 3.5%), Pakistan (9.7 million, 2.7%), the United States (9.6 million, 2.6%), China (4.1 million, 1.2%), Indonesia (3.2 million, 0.9%), Nepal and Colombia (3.0 million, 0.9% each) and Madagascar (2.5 million, 0.7%; Sinha *et al.*, 2018).

Data from previous studies suggest that smoking is the predominant form of tobacco used in industrialised countries (NCI and CDC, 2014). Despite this, SLT use is prevalent in many European, American and Western Pacific countries. A recent review by Leon *et al.*, (2016), involving 18 European countries, revealed that the highest prevalence of SLT use was observed in Sweden (12.3%; 20.7% males, 3.5% females). Among other European countries, the highest rate of SLT use was observed in Poland (5.5%), Spain (2.5%), the Czech Republic (2.1%) and Finland (2.0%). In the Americas, the highest rate of use was seen in the United States (3.2%) and Micronesia (11.4%) in the Western Pacific (NCI and CDC, 2014).

Table 4: Smokeless tobacco prevalence and the number of users, 15 years of age or more, among WHO regions and the World Bank country income group, 2007–2017

	Average prevalence rate (%)			**Estimated no. of SLT users (millions)**		
WHO regions	**Males**	**Females**	**Both sexes**	**Males**	**Females**	**Both sexes**
All	8.4	4.6	6.5	237.3	129.4	366.7
African	2.9	2.4	2.7	8.0	6.8	14.8
Americas	1.8	0.2	1.0	7.5	0.7	8.2
Eastern Mediterranean	4.0	1.3	2.7	8.4	2.6	11.0
Europe	1.6	0.3	0.9	6.9	1.4	8.3
South-East Asia	27.7	16.4	22.1	191.8	109.5	301.4
Western Pacific	1.8	1.1	1.4	14.7	8.5	23.1
World Bank country income group						
All	8.4	4.6	6.5	237.3	129.4	366.7
High-income	1.6	0.2	0.9	9.2	1.3	10.5
Upper middle-income	1.7	0.9	1.3	18.5	10.0	28.5
Lower middle-income	20.3	11.6	16.0	202.9	113.9	316.9
Low-income	4.1	2.4	3.2	6.7	4.1	10.8

(Source: WHO, 2018a)

The WHO's recent report on global smoking prevalence showed a declining trend: 25.7% in 2000 to 19.8% in 2015 and this is projected to be 17.1% by 2025 (WHO, 2018a). However, rates of SLT use have not seen a similar decline. Instead, SLT prevalence in the SEAR has thrived and in countries such as Bangladesh, SLT prevalence is still higher than smoking prevalence (Sinha *et al.*, 2015). Based on the recent Global adult tobacco survey (GATS), the overall prevalence of SLT in Bangladesh fell by 7.14%, from 27.2% in 2009 to 20.06% in 2017. However, the overall prevalence of SLT in Bangladesh remained high (20.6%) compared to smoking tobacco (18%) (GATS, 2017). Similarly, in India, the two waves of GATS also showed that SLT prevalence was declining, from 25.9% (2009-2010) to 21.4% (2016-2017), with SLT remaining the major form of tobacco use. 10.7% of adults are currently smoking tobacco compared to 21.4% using SLT (Chaturvedi *et al.*, 2017). Therefore, potentially, there is the possibility that the smoking epidemic could become an SLT epidemic in this region.

1.2 Smokeless tobacco use in Bangladesh

1.2.1 Types of smokeless tobacco used in Bangladesh

A wide variety of SLT products are used in Bangladesh, including unprocessed, processed and manufactured products, which vary significantly in their composition, method of preparation and consumption pattern (Huque *et al.*, 2017). Recent studies suggest that sun-dried tobacco leaves (locally known as sadapata), zarda and gul are the most commonly used SLT products in Bangladesh (Zaman *et al.*, 2014; Hossain *et al.*, 2014a). Table 5 provides the names of commonly used SLT products in Bangladesh and their prevalence among adults.

1.2.2 The prevalence, trends and characteristics of smokeless tobacco users

Bangladesh has a long history of tobacco use. Overall, 35.3% adults (37.8 million; 46.0% male, 25.2% female) use various forms of tobacco (WHO, 2017). Based on the recent GATS report (2017), 20.6% of Bangladeshi adults (24.8% female, 16.2% male) use SLT. Overall, one-quarter of Bangladeshi adults use SLT, making it the main form of tobacco use in Bangladesh. During 2004–2009, SLT use in Bangladesh increased by 7.5% or 9 million users (from 17.2 million to 25.9 million). However, as mentioned previously, due to government initiatives during 2009–2017, overall SLT use fell by 5.8% and was greater among men (decreased by 10.2%) compared to women (decreased by 3.1%; WHO, 2017).

Table 5: Commonly used smokeless tobacco products in Bangladesh: composition, production, consumption and prevalence

SLT products	Compositions	Production	Consumption	Prevalence adults (%)
Zarda	Tobacco, lime, spices, vegetable dye and areca nuts	Manufactured commercially	Chewed with BQ	24.3
Gul	Tobacco powder, molasses	Manufactured commercially	Applied to teeth and gum	5.3
Sada Pata	Sun-dried or cured raw tobacco leaf	Processed but unpacked, homemade	Chewed with betel leaf, lime and areca nut	1.8
Khoinee	Tobacco, slaked lime, menthol, flavourings and areca nut	Manufactured commercially or prepared by the user	Kept in the mouth between the lips and gum	1.5
Any form of SLT		Manufactured commercially or processed but unpacked or prepared by the user	Same as above	27.2

(Source: Huque *et al.*, 2017)

The majority of SLT users in Bangladesh use products regularly, with 65% of the current SLT users (both men and women) being daily users (NCI and CDC, 2014). However, the combined use of smoking and SLT remains low in Bangladesh, with only 6.8% of Bangladeshi adults being dual users (13% male, 0.70% female). Regarding the age of initiation, Bangladeshi adults begin using SLT late compared to smoking tobacco. The previous GATS Bangladesh study showed that the mean age of smoking tobacco initiation in Bangladesh was 18.8 in 2009. However, the study did not report the SLT initiation age. Several other studies reported the key difference between SLT and smoked tobacco initiation in Bangladesh. A population-based prospective study of 19,934 Bangladeshi adults found that the mean age of SLT initiation among Bangladeshi adults was 31 years (Heck *et al.,* 2012). Another large population-based cross-sectional study of 6,178 individuals aged ≥13 years observed a similar trend, as the average age was 35.0 years (mean±SD, 35.1±13.6 years), although the use of SLT started somewhat earlier in men (33.7±14.8 years vs 37.5 ±10.9 years) (Mia *et al.,* 2017). The overall quit ratio of SLT use in Bangladesh was low (5.5%) (WHO, 2009).

In Bangladesh, the higher prevalence of SLT among the older population remains a public health issue. The popularity of SLT use in Bangladesh rises steadily with age. Only 6.6% of individuals aged 15–24 years use it, compared to 56.4% of those aged 65 years and above (WHO, 2009). A recent International Tobacco Control survey (ITC) report from Bangladesh showed that SLT use rates increase with age, with 36% of adults aged 55 years and older using SLT compared to only 8.5% of adults younger than 25 years (Abdullah, *et al.,* 2014). The same trend was also observed among adolescents, with 8.5% of youths aged 11–12 years using tobacco compared to 16.2% of those aged 16 and older (Kabir *et al*., 2015). However, the information related to these rates was not exclusive to SLT use as both smoking and SLT were included in the data.

There are gender differences in tobacco use is observed in Bangladesh with the majority of SLT users being women, which has been documented in previous studies. A survey among 35,000 Bangladeshi adults showed that men are twice as likely to use tobacco; however, when different types of tobacco use were considered, women were less likely to smoke tobacco or use smoking and SLT in combination and more likely to use SLT (Flora *et al.,* 2009).

Most SLT users in Bangladesh came from a low socio-economic background and more than half of SLT users have no-formal education. There was a higher rate of SLT use (52.1%) among individuals from lower socio-economic status (SES) households (<5,000 BDT per month; £47) compared to 7% from higher SES households (>10,000 BDT per month; £94). A higher rate of SLT use was observed among individuals from households with illiterate heads who owned less than 200 decimals of land (Choudhury *et al*., 2007; Mia *et al*., 2017). SLT use was also more prevalent among the rural population, who were 1.5 times more likely to be SLT users compared to the urban population (Flora *et al*., 2009).

1.2.3 Key factors associated with the high prevalence of smokeless tobacco use in Bangladesh

1.2.3.1 Socio-cultural factors

Socio-cultural factors play a key role in risk-taking behaviour. Early studies suggest that society provides the context for its members in which their behaviour is shaped and conducted in certain ways (Mane, 1994). Society and culture influence the initiation or cessation of tobacco use and focuses on which tobacco is deeply embedded in the value system. Several socio-cultural norms and factors influence SLT use and can be classified into three major factors: social acceptability, religious beliefs and perceived health benefits (Auluck *et al.*, 2009). The above framework is used to understand how socio-cultural factors shape SLT use in Bangladesh.

Social acceptability

In Bangladesh, using SLT is regarded as a shared social activity that is performed with friends, relatives and family members and it has been integrated into social gatherings, such as festivals, weddings and religious gatherings (Sansone, 2014). Therefore, the relationship between social rituals and the use of SLT has been passed on from generation to generation as a cultural tradition (Kakde *et al.,* 2012). However, in the case of smoking, there is not the same level of social acceptance and inclusion. In Bangladeshi society, traditional values do not allow or strongly discourage smoking by women (Gupta and Ray, 2003). For Bangladeshi men, smoking is associated with their male identity and therefore viewed as a normal social activity, whereas for women, it is regarded as bad and disrespectful (Bush *et al.*, 2003). It is more likely that women who smoke publicly will be noticed compared to men and many of them avoid smoking to avoid the negative perception of their family members and elders. However, SLT is highly prevalent among Bangladeshi women as it is more acceptable than smoking and easier for women to conceal, due to the lack of odour and smoke.

The high prevalence of SLT use in Bangladesh is also associated with family tradition, as many users start using SLT as a result of being influenced by their family members (Rahman *et al.*, 2015). In Bangladeshi society, younger people hesitate to smoke in front of their parents or seniors. However, SLT is an exception and chewing pan or betel leaf along with tobacco products is regarded as normal social behaviour and considered to be a symbol of hospitality in the rural areas of Bangladesh. Even individuals who have few resources feel embarrassed if they cannot offer SLT to a guest in their home (Islam and Al-Khateeb, 1995).

Religious beliefs

Tobacco use is discouraged by Islam. Nevertheless, SLT use is still common in Bangladesh, a Muslim-majority country. Misinterpretation of tobacco use under Islam, such as allowing people to use SLT if they are not addicted to it, leads to SLT initiation and dependency. In Islam, any form of tobacco use is considered to be *haram* or forbidden (Albar, 1994). Being Muslim is considered to be a protective factor against SLT use (Etu *et al.,* 2017). However, this statement is dubious. Unlike alcohol, tobacco products are not specifically prohibited or restrained by Islam, but the Koran does prohibit intoxicants and addictions.

An earlier study of Bangladeshi and Pakistani adults found that there are conflicting viewpoints on whether it is religiously acceptable for Muslim men to smoke and the degree to which smoking is permitted in Islam (Bush *et al.*, 2003). Many felt it was acceptable for someone who is neither addicted nor intoxicated with tobacco products to smoke. Perhaps for this reason, Muslim men are more likely to smoke and Muslim women are more likely to chew tobacco than Hindu women (Bush *et al.,* 2003). A previous study from Bangladesh also found a substantial relationship between religion and BQ chewing, with Hindus being more likely to chew BQ with tobacco than other religions (Flora *et al.*, 2012).

Hinduism is the second-most commonly practised religion in Bangladesh. For many Hindu religious followers, betel nuts (one of the key ingredients of BQ, which is used with SLT) are viewed as a fruit of divine origin. They are seen as an auspicious ingredient in Hinduism and taken along with betel leaf in many religious ceremonies. They are also considered as a food for God and offered to God while offering prayers. People believe that God blesses the fruit, which is later shared with their admirers with betel leaf and SLT as a health aid (Auluck *et al.*, 2009).

Awareness and misconceptions

Overall awareness of the adverse effects of SLT use is remarkably poor in South Asian countries and is mirrored by the high SLT use rates in this region. Misconception and myths are widespread, as many users think SLT has medicinal benefits for treating common discomforts, such as toothache, headache and stomachache. These misconceptions prompt adults to offer SLT to non-users and even children (Gupta and Ray, 2003). Myths and misconceptions related to SLT use is common in Bangladesh and widely prevalent in rural areas. A recent study conducted by Shahjahan *et al.,* (2017) revealed that Bangladeshi SLT users perceived SLT as less harmful than smoking. Many Bangladeshi women use SLT during pregnancy to avoid morning sickness. In rural areas of Bangladesh, it is widely believed that SLT use also relieves toothache (Rahman *et al.*, 2015). Many Bangladeshi women believe that using BQ helps keep their gums and teeth healthy, helps them to manage their weight and enhances their mood (Wright *et al.,* 2013). Low awareness of risk combined with misconceptions about the benefits and harmlessness of SLT use contribute to social acceptability and high SLT use in Bangladesh.

1.2.3.2 Smokeless tobacco control policies and measures in Bangladesh

Bangladesh is a country with a huge burden of tobacco-linked ill health, as a result of the country's large production and consumption of various tobacco products. According to Tobacco Atlas, 85,000 metric tonnes of tobacco were produced in Bangladesh in 2014, with 31,161 hectares of agricultural land devoted to tobacco cultivation (Tobacco Atlas, 2018). Hence, the WHO (2015b) recognised Bangladesh as one of the five countries of the Bloomberg Initiative to Reduce Tobacco Use. With its long-standing commitment to tobacco control initiatives, Bangladesh was the first developing country to sign the WHO Framework Convention on Tobacco Control (FCTC) in 2004 (WHO, 2015b). Bangladesh enacted its first Tobacco Control Act (TCA) in 2005 and enforced it in 2006 (Nargis *et al.*, 2014a). However, SLT was not incorporated into the TCA in 2005.

According to the TCA of 2005, in Bangladesh, *'tobacco product means anything produced from tobacco which can be inhaled through smoking, and also includes Biri, Cigarette, Cheroot, Cigar and mixture used by pipe'* (Alam, 2018, p. 10) However, in 2013, the Bangladesh government amended the law and included SLT under the definition of tobacco. Based on the amendment, '*tobacco products means any product made from tobacco, tobacco leaf or its extract which can be sucked or chewed, or inhaled through smoking, and shall include bidi, cigarette, cheroot, gul, jarda, khoinee, sadapata, cigar and mixture used in pipe or hukkah'* (Alam, 2018, p. 10). The comprehensive action against SLT use was initiated in 2015 when the newly revised law was enforced.

In their study, Khan *et al.,* (2014) developed a framework for SLT control policy, based on the WHO MPOWER strategy, which included (a) awareness-raising campaigns, (b) surveillance and information gathering to inform policy, (c) regulating production, distribution, marketing, and sales, (d) raising taxes and using other fiscal measures and (e) providing services to support people who wish to quit. Bangladesh's key policy initiatives to deal with the SLT burden were outlined using this framework. These are described below.

Awareness-raising campaigns

Although extensive evidence has been used to outline the dangers of tobacco use, very few users fully grasp the health risk associated with tobacco use. The general attitude to tobacco is that, although it is unsafe, it is merely a bad habit that they indulge. As mentioned earlier, in Bangladesh, SLT is deeply rooted in the local culture and rural population (Hossain *et al.*, 2016). However, most of this population are unaware that SLT use increases their risk of oral pre-cancerous lesions, oral malignancy and heart disease (Hossain *et al.*, 2016). Anti-SLT campaigns are limited or non-existent in Bangladesh (Khan *et al.*, 2014) even though the government has previously launched a national anti-tobacco campaign. However, many of these actions were merely devoted to the dangers of SLT use.

Surveillance and information gathering to inform policy

According to the WHO (2008), an efficient monitoring system would track several indicators, such as the prevalence of tobacco use and the impact of policy intervention and tobacco industry marketing and promotion. Bangladesh has introduced periodic national-level surveys in partnership with the WHO: the GATS, the Global School Personnel Survey (2007) and the GYTS. These surveys reveal the prevalence of SLT use, as well as other cessation indicators. However, such data does not entail sufficient monitoring of the impact of SLT policy intervention and tobacco industry marketing and promotion. The key reason for this is that the TCA 2005 did not include SLT as a tobacco product.

Regulating production, distribution, marketing and sales

According to a recent report by the Director of Agricultural Expansion of Bangladesh, 70,000 hectares of land was used to harvest tobacco during 2012–2013 and this increased to 108,000 hectares in the 2013–2014 farming season (Genilo and Sharif, 2016). According to the new amendment of tobacco control law, a licence is required to produce and sell SLT products in Bangladesh. However, the law is only relevant to packaged products (Khan *et al.*, 2014). Other locally or homemade products, such as loose tobacco (locally known as sadapata), are not covered by the act. The widespread availability of homemade SLT products in the rural markets and their low price make SLT control strategies ineffective.

Based on the new TCA 2013, SLT manufactures must write health warnings and graphic images that cover at least 50% of the product packaging. However, Siddiqi *et al.,* (2016a) identified 43 different SLT products in a local market, and only 53% of them had handwritten health warnings, only 41.2% had printed ingredients and only 57%

mentioned that tobacco was one of the ingredients. The poor implementation of text warnings, coupled with the high illiteracy rate in rural areas, are likely to contribute to the current poor understanding of the specific risks associated with SLT use (Barkat *et al.,* 2012).

The new TCA 2013 has prohibited the advertising of SLT products. This includes the print and electronic media, as well as any other form of advertising, such as point of sale or billboards (Huque *et al*., 2017). The law also means there are fines for violations of direct advertising bans, although poor implementation of the law has been reported, and point-of-sale advertising is still widely seen, which clearly violates the law (Bhuiyan *et al*., 2015).

The extended TCA 2013 also prohibited the buying and selling of SLT by minors. This complies with the WHO FCTC Article 16 that mentions the banning of SLT sales to and by minors. However, buying and selling SLT by minors is still rampant, probably because of ignorance and a lack of awareness of the law (Alam, 2018). Hence, a comprehensive policy formulation with effective interventions and proper enforcement of the law is required to ensure that minors do not possess or sell SLT products.

Raising taxes and using other fiscal measures

The Government of Bangladesh has imposed a variety of taxes on tobacco products (cigarettes, bidis, SLT and pipe tobacco), including supplementary duties, duties on imported and exported tobacco products and value added tax (VAT) on the retail prices of all kind of tobacco products. However, tax on SLT products remains low in Bangladesh, compared to tax on smoked tobacco (Huque *et al.*, 2017). According to the WHO, the single most cost-effective way to reduce tobacco use would be to significantly increase tobacco product prices and taxes, particularly among vulnerable groups (such as adolescents) (Nargis *et al.*, 2014a).

Recently, the Government of Bangladesh increased the excise tax on SLT (Table 6). Taxes on cigarettes range from 66% to 80% of the retail price; in comparison, taxes on the most popular SLT products in Bangladesh, zarda and gul, were raised to 116%. Despite the SLT tax rate being a positive step, the real flaw is that the tax base for SLT is the 'ex-factory' price, which is far less than the retail price. The prices of SLT products in Bangladesh have remained low compared to the lowest price of smoking tobacco. On average, the price of zarda (the most commonly used SLT product in Bangladesh) per gram is less than half of the price per stick of the cheapest brand of cigarette.

Table 6: History of tax on smokeless tobacco products in Bangladesh

Year	Tax on SLT*			Total (%)	Total tax collection from VAT and SD (million Taka)
	SD (%)	VAT (%)	Health development surcharge (%)		
2010-2011	20	15	-	35	57.2
2011-2012	30	15	-	45	79.5
2012-2013	30	15	-	45	87.5
2013-2014	30	15	-	45	106.3
2014-2015	60	15	1	76	175.5
2015-2016	60	15	1	76	69.2 (up to October, 2015)
2016-2017	100	15	1	116	

*The tax base is ex-factory price. SD: Supplementary duty, SLT: Smokeless tobacco, VAT: Value added tax

(Source: Huque *et al.*, 2017)

The effectiveness of the higher price and tax strategies to control SLT use has also been hindered by the smuggled and counterfeit SLT products in the Bangladeshi market. An estimated 12% of SLT products in the Bangladeshi market come from neighbouring countries, with 45% being smuggled through land ports and 26% through airports (Siddiqi *et al.,* 2016a; Huque *et al.,* 2017).

Providing services to support people who wish to quit

According to the WHO FCTC Article 14, every government should sponsor tobacco cessation services and provide support to those who are tobacco-dependent and wish to quit using tobacco products (Nilan *et al*., 2017). However, LICs have far less support for tobacco cessation compared with HICs (Siddiqi *et al.,* 2017). Recent results from the

GATS from Bangladesh showed that over 50% of tobacco users want to quit SLT (WHO, 2017). Despite the high prevalence of SLT use and its related burden, Bangladesh does not offer SLT cessation services in public healthcare facilities.

SLT use causes a higher level of dependency and highlights the importance of an effective SLT cessation service. Cotinine is a recommended biomarker used to measure the dependence of SLT users. A study conducted by Huque *et al.*, (2016) found high cotinine concentration levels among Bangladeshi SLT users, indicating a high level of addiction. Moreover, SLT users were found to have a higher level of salivary cotinine compared to smokers (Patel *et al.,* 2017). The level of nicotine is also reported to be higher in SLT compared to smoking and as high as 74mg/g in SLT (Nasrin *et al.,* 2020). The nicotine concentration in the tobacco of traditional bidi is 21.2 mg/g, 16.3 mg/g in commercial filtered cigarettes and 13.5 mg/g in unfiltered cigarettes (Malson *et al.,* 2001). The high level of nicotine causes a high level of addiction and warrants an intensive cessation service.

The lack of effective SLT cessation interventions is a key issue in public health services. A recent study conducted by Siddiqi *et al.,* (2016b) indicated that evidence of SLT cessation interventions is limited compared with smoking tobacco and this is further complicated by the heterogeneity of SLT products. The provision of some interventions, such as nicotine replacement therapy, is extremely low or non-existent in Bangladesh.

1.3 Adolescents and smokeless tobacco

1.3.1 Global prevalence and current trends

Based on the GYTS data, an estimated 13.4 million or 3.6% of the world's population aged 13–15 years are using SLT products. Similar to adult SLT use, adolescents from the SEAR had the highest prevalence of SLT use (7.2%) and accounted for 60% of global SLT users aged 13–15 years (Table 7; WHO, 2018a). Nearly 13% of adolescent users live in the African region and 12% in the Eastern Mediterranean region (Sinha *et al.*, 2018). Except for Europe, every WHO region had at least 1 million adolescent SLT users (Table 7) Adolescent SLT use was greater in LMICs and LICs (10.5 million) than HICs and upper-middle-income countries (UMICs) and accounted for 78.4% of global users (WHO, 2018a).

Regarding gender, more boys (8.8 million) than girls (4.6 million) use SLT, and the ratio was just under two boy users for every girl user (WHO, 2018a). The highest SLT use rates for both boys (9.4%) and girls (4.8%) were also observed in South-Asia. A recent review of the GYTS data from 106 countries, representing 72.5% of the global population, showed that the highest rate of SLT use among boys and girls was from Micronesia, at 26.4% and 21.7%, respectively (Sinha *et al.*, 2017). In the SEAR, Bhutan had the highest SLT use rates for both boys and girls, at 25% and 18.9%, respectively, followed by Nepal with 19.7% and 12.9%, respectively (Sinha *et al.*, 2017).

Table 7: Smokeless tobacco rates of use and the number of users aged 13–15 years among WHO regions and World Bank income groups from 2007 to 2017.

Average prevalence rate (%)				**Estimated no of SLT users (millions)**		
WHO regions						
	Boys	**Girls**	**Both sexes**	**Boys**	**Girls**	**Both sexes**
All	4.6	2.6	3.6	8.8	4.6	13.4
African	2.2	1.6	1.9	0.8	0.5	1.3
Americas	3.2	1.6	1.9	0.8	0.4	1.2
Eastern Mediterranean	4.5	3.1	3.8	0.9	0.6	1.4
Europe	1.1	3.1	3.8	0.2	0.1	0.3
South-East Asia	9.4	4.8	7.2	5.4	2.5	7.9
Western Pacific	2.2	1.4	1.8	0.8	0.5	1.3
World Bank country income group						
All	4.6	2.6	3.6	8.8	4.6	13.4
High-income	1.5	0.6	1.0	0.4	0.1	0.5
Upper middle-income	2.7	1.6	2.2	1.5	0.8	2.4
Lower middle-income	7.1	3.8	5.5	6.2	3.1	9.4
Low-income	3.0	2.1	2.6	0.7	0.5	1.1

(Source: WHO, 2018a)

1.3.2 Smokeless tobacco use among adolescents in Bangladesh

Data related to adolescent SLT use in Bangladesh is limited, as only national representative data is available from the GYTS. Based on the recent GYTS report (2013), rates for current and ever SLT prevalence among school students aged 13–15 years were 4.5% and 10.1%, respectively (WHO, 2015). The prevalence of SLT use was higher among boys (5.9%) than girls (2.0%).

Bangladesh did not observe any significant change in adolescent SLT use between 2007 and 2013; in 2007, it was 4.9% (5.8% boys vs 4.2% girls; WHO, 2009). A similar trend was observed in several South-East Asian countries: no significant change was observed in the last 6 years in India (2006–2009), Sri Lanka (2007–2011) or Myanmar (2007–2011). However, a significant rise in adolescent SLT use occurred from 2009 to 2013 in Bhutan (9.4% to 23.2%) and Nepal (6.1% in 2007 to 16.2% in 2011; Figure 2; Sinha *et al.*, 2014).

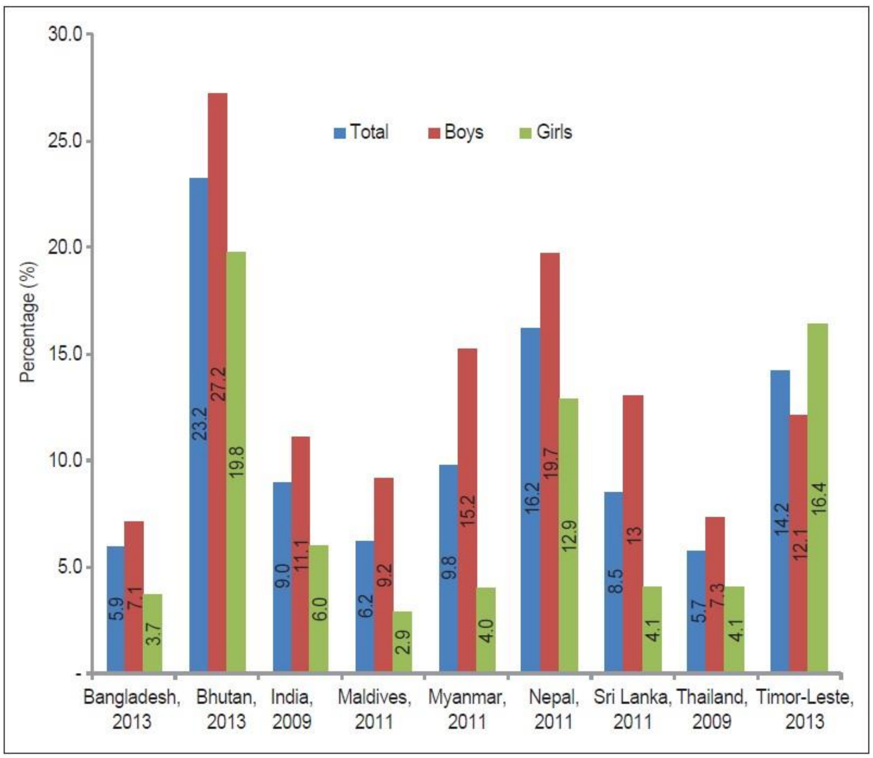


Figure 2: Smokeless tobacco use in South-East Asian youth (school students aged 13–15 years). (Source: Sinha *et al.*, 2014).

1.3.3 Implications of adolescent smokeless tobacco use

1.3.3.1 Risk of transition to smoking

The consequences of adolescent SLT use are different compared with adults. SLT can be a gateway drug that leads to smoking and other substance use. To examine this issue, Tomar (2003) conducted a study among a US cohort of 7,900 male adolescents, aged 11–19 years. The study's results showed that participants who were regular SLT users at the beginning of the study were three times more likely to be current smokers four years later, OR = 3.45, 95% CI [1.84, 6.47]. Overall, over 40% of baseline current SLT users became smokers over the four-year period, suggesting that SLT may be a starter product for smoking among young US adolescents.

Tam *et al.,* (2015) found in their systematic review that 16.6%–25.5% of adolescents who are only SLT users eventually switched to exclusive cigarette smoking. This issue was further investigated by Severeson *et al.*, (2007), who assessed the risk of smoking uptake over a 2-year period in adolescent boys (grades 7 and 9) who had used SLT. The study established that the status of SLT use was a significant and robust predictor of weekly smoking after 2 years, OR = 2.55, 95% CI [1.45, 4.47], $p < .001$ (Severeson *et al.*, 2007). Similar findings were reported in the US Youth Behaviour Survey (2011), a national survey that showed adolescents who were SLT users were nearly four times more likely to be a smoker, OR = 3.92, 95% CI [2.89, 5.31], $p < .0001$, and binge drinker, OR = 2.50, 95% CI [1.82, 3.45] (Wiener, 2013).

1.3.3.2 Biological implications

Two biological implications of adolescent SLT use are noted in the literature: addiction and health consequences.

Addiction

When using SLT, an adolescent is exposed to nicotine (NCI and CDC, 2014), a highly addictive chemical that leads them to keep using the product (Post *et al.*, 2010). Once SLT is consumed by the adolescents, components in SLT, such as fibreglass, cause tiny incisions in the oral tissues that allow nicotine to enter the bloodstream. An average pinch of SLT can deliver approximately the same amount of nicotine as three cigarettes (Hatsukmani *et al.*, 2007). The amount of nicotine in SLT products varies substantially among products and countries.

In developing countries, manufacturers rarely disclose the nicotine content in SLT products, but it is highly likely that these SLT products contain high levels of nicotine (Ayo-Yusuf *et al.,* 2004). High concentrations of nicotine in SLT products have a calming effect and the continued use of SLT leads to nicotine dependency. After extended use, adolescents start to develop a tolerance for their current intake of nicotine and begin to crave larger amounts. This leads them to increases the portion of SLT or move to a stronger brand with a higher concentration of nicotine (Griesler *et al.*, 2016). Eventually, the adolescent reaches a stage where nicotine addiction has both physiological and psychological effects (Ebbert *et al.*, 2012).

Health consequences

Regardless of whether they are addicted or not, regular use of SLT can cause adolescents to develop the signs and symptoms of oral diseases, such as gum disease, oral leukoplakia (white lesions) or dental caries. Several studies have described the association between SLT use and the increased risk of oral lesions among adolescents. A large US national survey of oral health in school students reported that 1.5% of the students had SLT-related oral lesions. These oral lesions were strongly associated with the duration of their use, including monthly frequency and daily minutes of snuff and chewing tobacco use (Tomar *et al.,* 1997). In another survey of 270 middle school male students in the Kingdom of Saudi Arabia (KSA), it was found that nine out of ten students had oral lesions related to SLT use (Al-Agili and Park, 2013).

Oral leukoplakia is a common oral lesion reported among SLT users, including adolescents. A study of 1,116 US adolescents showed that oral leukoplakia was present in 13% of current SLT users (Creath *et al.*, 1991). Further, the results demonstrated that both the dose-response relationship and risk of oral leukoplakia increased with regular SLT use, as years of SLT use meant that larger weekly quantities were consumed. The development of oral cancer from SLT use is a slow process; it typically takes 20 to 50 years of use to cause malignant changes in the oral lesions. Therefore, by using SLT at an early age, these adolescents are at risk of developing cancers in adulthood.

SLT use in adolescence is likely to be associated with an increased risk of dental caries. A large longitudinal study of 10,068 adolescents, aged 16–19 years from Sweden, showed that SLT is associated with an increased risk of dental caries during adolescence (Holmen *et al.*, 2013). However, an earlier study from the US found there was insufficient evidence to support any associations between SLT use and gingivitis, periodontitis or dental caries (Weintrub and Burt, 1987). In contrast, a recent study from India supported the association between SLT use and dental caries in adolescents (Lashkari and Sjukla, 2016). The level of sugar, sweeteners and other additives contained in SLT products varies among the types, brands and regions, and this might explain the different findings regarding the incidence of dental caries related to SLT use (Hellquvist *et al.*, 2015).

1.4 The public health burden of smokeless tobacco use

SLT use is a global public health challenge that affects 140 countries, representing 93.8% of the total world population. An estimated 348,798 deaths in 127 countries have been associated with SLT use (Siddiqi *et al*., 2020). SLT products are scientifically proven to be as addictive as smoked tobacco (Mehrotra, *et al.,* 2019). Over 30 types of high concentration carcinogens can be found in SLT, and their use in the oral cavity causes oral pre-cancerous lesions, oral cancer, oesophageal, pharyngeal, and pancreatic cancers (NCI and CDC, 2014). In 2017, at least 2.5 million DALYs and 90,791 lives were lost across the globe due to oral, pharyngeal and oesophageal cancers that can be attributed to SLT use (Siddiqui *et al.,* 2020). Given that the majority of SLT users live in the SEAR, 85% of the cancer-related burden is from this region (Siddiqui *et al*., 2015), with the highest impact being in India, Bangladesh and Pakistan (NCI and CDC, 2014).

SLT products are regarded as a cheap alternative to smoking that offer the same nicotine kicks and lead to higher nicotine addiction (Rout and Arora, 2014). Compared with smoking, SLT products are manufactured, stored and consumed in countless ways, and inadequate regulatory frameworks in high-use countries have made SLT control particularly difficult (Sinha *et al*., 2018a).

When compared with other SLT use regions, the SEAR faces unique issues, including products with various components, unregulated market forces and the sale of SLT in the informal setting (Sinha *et al.,* 2015). Bangladesh is one of the lower-middle-income countries (LMICs) in the SEAR with high population density, poverty, a paucity of healthcare resources and low levels of health literacy. Bangladesh has been facing severe health consequences and the economic burden of tobacco use (Faruque *et al*., 2019) and is now the home of nearly 22 million SLT users (WHO, 2017). The burden of SLT use-related diseases in Bangladesh is substantial. SLT use is responsible for 404, 460 DALYs lost and 16,947 deaths from non-communicable diseases (NCDs), such as cancers and heart diseases (Siddiqi *et al*., 2020).

1.4.1 The non-communicable disease burden and smokeless tobacco use

NCDs are one of the major public health challenges in the 21st century (Baker *et al.*, 2016). Annually, 16 million deaths are attributable to four major NCDs (cardiovascular diseases, cancers, chronic respiratory diseases and diabetes), which account for 82% of all NCD-related deaths (WHO, 2018b). It is predicted that by 2025, the global economic cost related to these four major NCDs will reach nearly 52 trillion US dollars (Allen *et al.*, 2017). NCDs disproportionately affect LMICs, as people from LMICs are four times more likely to die from NCDs compared with high-income countries (WHO, 2018b).

Globally, 9.6 million deaths in 2018 were attributable to cancer (IARC, 2018), and the burden of cancer incidence is growing and is much higher in LMICs (Fitzmaurice *et al.,* 2017). To achieve the Global Monitoring Framework of reducing NCD-related mortality by 25% by 2025, it is necessary to further identify the major causes of cancers (Sinha, Abdulkader and Gupta, 2016). Oral cancer is highly related to SLT use and is one of the top causes of cancer in the SEAR (Sinha *et al.,* 2016). More than half of the oral cancer cases in the world occur in Asia and almost 11% of these cases are from the SEAR (Cheong *et al.,* 2017).

Like other developing countries, Bangladesh has been experiencing an epidemiological transition from communicable diseases to NCDs (Rahman and Zaman, 2008). In Bangladesh, NCDs are the primary cause of morbidity and mortality, accounting for 61% of total deaths (Biswas *et al.*, 2017). The four major NCDs mentioned above have become a major health problem (Zaman *et al.,* 2016). Several modifiable NCD risk factors, such as different forms of tobacco use, are highly prevalent in Bangladesh. With the current trend of tobacco use in Bangladesh, it is highly likely the prevalence and mortality attributable to NCDs will increase in the future (Bleich *et al.,* 2011).

Oral cancer is one of the major causes of NCDs and the second-most common cancer for both men and women in Bangladesh. In Bangladesh, an estimated 13,401 new cases are diagnosed every year and 8,507 people die due to oral cancer, which accounts for nearly 9% of all cancer cases and 8% of cancer-related deaths (IARC, 2018). Also, SLT is the main form of tobacco used by Bangladeshi women, whereas the dual use of SLT and smoking is highly prevalent among men (Zaman *et al.,* 2014). Despite this, there is a lack of etiological research on SLT and oral cancer in Bangladesh.

1.4.2 Research priority for non-communicable disease prevention

NCD prevention is one of the sustainable development goals (SDGs), which is to reduce the premature mortality from NCDs to one-third by 2030 (Bongaarts, 2016). Also, the third objective of the WHO's global NCD action plan 2013–2020 was to create health-promoting environments that reduce the modifiable risk factors for NCDs and underlying social determinants (WHO, 2013a). Although deaths from NCDs mostly occur in adulthood, exposure to risk factors, such as SLT use, begins in childhood and then builds up throughout life (Kovacs *et al.,* 2014). Hence, regular monitoring of all forms of adolescent tobacco use and determinants are essential in order to plan effective interventions that prevent tobacco-related harm.

Another key concept of preventing NCDs is the generation of study evidence that is related to both the causes and risk factors of these deadly diseases (Tripathy, 2018). Although it is well known that lifestyle risk factors are linked to the major NCDs, there remains a knowledge gap that is preventing effective public health action (Allen *et al.,* 2017). In many LMICs, the actual population burden of some NCDs is still unknown and even if it was known, the causes are not (Ebrahim *et al*., 2013). There is still a need for an accurate assessment of the magnitude of the NCDs in country-specific settings, specifically in countries where little research has been conducted on chronic NCDs and resources for such research is limited (Sharma, 2017).

Surveillance of non-communicable disease risk factors

The WHO recommends that the surveillance of major risk factors of NCDs, such as SLT use, play an imperative role in the prediction of the future burden of NCDs (Kabwama *et al.,* 2016). Lifestyle risk factors, such as SLT use, is modifiable. To pave the way for a better and healthier life in adulthood and prevent NCDs, the early recognition of such risk factors in adolescence is imperative (Dasgupta *et al.,* 2017). Also, most adults who develop nicotine dependency start by using SLT in their adolescence. Considerable evidence indicates that individuals who use tobacco in adolescence develop nicotine dependence in adulthood. The US Surgeon General Report (2012) suggests that a younger age of initiation is strongly associated with greater nicotine dependence in both young adulthood (18–25 years of age) and older adulthood (26 years of age and older; Benjamin, 2012). Hence, monitoring trends in adolescence SLT use can help to refine preventive efforts, particularly data about SLT use, initiation, accessibility and availability can provide vital information to monitor changes over time and inform enforcement, educational and prevention efforts (Lipari and Van, 2017).

Adolescent awareness of the modifiable risk factors of NCDs is a necessary precursor in the promotion of positive health-related behaviour and a public health priority (Kyle *et al.,* 2013). It is crucial that young people understand the risk factors of NCDs, as two-thirds of premature deaths in adults are associated with childhood conditions and behaviours that were initiated during adolescence (Baker *et al.,* 2016). Significant physical, psychological and social development occur during adolescence (Kyle *et al*., 2013). Risk-taking behaviour and susceptibility to social influence increase at a time when adolescents are becoming more independent through their decision-making and their actions (Wardle *et al.,* 2003). The initiation and persistence of risky behaviour affect an adolescent's perception of the risk related to a specific behaviour, as well as their understanding of the probable short- and long-term health risks that are linked with such behaviour (Larsman *et al.,* 2012).

While knowledge is important, it is rarely sufficient to change behaviour. It does not take into account the other complex influences on adolescent risk-taking behaviour. Knowledge is one of the key personal factors that play a role in the behaviour changes of adolescents. Other factors, such as social (interaction with others, including friends, family and the community), environmental factors (area of residence, schools, policy, technology) also play a vital role. There are several models and theories that enable us to understand adolescent behaviour and identify the underlying factors that influence it. 'Social cognitive theory' and 'Health belief model' are theories that take into account several factors that influence adolescents' behaviour. Details of their implications regarding adolescent SLT use is discussed in Chapter 2 of the literature review section.

Identification of non-communicable disease risk factors

Oral cancer is a significant public health burden and the 11th-most common cancer in the world (Sankaranarayanan *et al.,* 2015). Globally, oral cancer was responsible for an estimated 354,864 incident cases and 177,394 deaths in 2018 (based on the diagnostic criteria of the International Classification of Diseases, 10th edition C00-08). It accounts for nearly 2% of all cancer incidence cases and 1.9% of cancer-related deaths (Bray *et al.*, 2018). Approximately two-thirds of oral cancer cases occur in developing countries and the prevalence shows a significant geographical variation of as high as 20-fold (Warnakulasuriya, 2008).

Oral cancer is a multifactorial disease and its risk factors vary and operate differently for different population groups (Gupta and Johnson, 2014). Several independent risk factors of oral cancer have been identified. However, substance use, such as smoking, SLT use and alcohol consumption are the primary risk factors and account for 75%–90% of oral cancer cases (IARC, 2007; Gupta *et al*., 2012), while a poor diet has an additional relevant role (Gupta *et al.,* 2017). Occupational and viral factors have also been suggested, but their influence on oral carcinogenesis remains unquantified (Rodriguez *et al*., 2004).

There is a geographical variation of oral cancer incidence and mortality that is associated with variations of lifestyle risk factors within each region. SLT is one of the major risk factors of oral cancer in South Asia (Gupta and Ray, 2003). Over 90% of SLT users live in the SEAR, equalling 250 million users (Sinha *et al*., 2012). An estimated 22 million Bangladeshi adults are currently using different forms of SLT (WHO, 2017). Despite the high prevalence of oral cancer cases and SLT use, it is evident there has been a conspicuous lack of an epidemiological investigation of oral cancer risk factors.

1.5 Problem statement and rationale

In 2019, the Bangladesh government announced its vision to become a tobacco-free country by 2040 (WHO, 2019a). To achieve this ambitious target, the prevention of different forms of tobacco use among adolescents is essential. Recent data showed that the prevalence of SLT among Bangladeshi adolescents (4.5%) was double that of cigarette smoking (2.1%; WHO, 2015). In Bangladesh, SLT consumption by adolescents is socially acceptable but smoking is regarded as a negative behaviour (Hussain *et al.,* 2017). SLT use is incorporated into traditional values, social norms, beliefs, spirituality, festivals and many more aspects of Bangladeshi life (Huque *et al.,* 2017). Parents encourage their children to use SLT, as it is a social norm (IARC, 2007). Thus, adolescents are at a higher risk of becoming regular SLT users in adulthood. Despite this, information related to adolescent SLT use in Bangladesh is limited.

The Global Youth Tobacco Survey (GYTS) reported on SLT prevalence among Bangladeshi adolescents. However, this report had several limitations. The core questionnaire of the first phase of the GYTS (1999–2008) only focused on the use of smoked tobacco and did not cover SLT use. In the second phase of the GYTS (2008 onwards), the SLT module was included in the questionnaire, which included 17 items related to the current pattern of use, access and the availability of SLT products, future intention to use them and perceptions about their addictiveness. However, both the Bangladesh GYTS 2009 and 2013 only reported on adolescent SLT prevalence, so no other factors were explored in the reports. Moreover, the questionnaire did not include any items related to adolescents' knowledge and awareness of the ill-effects of SLT use.

To prevent tobacco initiation among adolescents, accessibility and availability should be restricted, as ease of access is significantly associated with tobacco initiation among adolescents (Goel, Kumar and Singh, 2016). Legal restrictions on minors' access to tobacco could prevent tobacco initiation among this vulnerable group (Gendall *et al.,* 2014). Bangladesh has recently passed a law banning the sale of tobacco (including SLT) to minors in 2013 (WHO, 2013b), which only came into effect in 2015. Periodic measurement of adolescents' compliance with existing tobacco control laws must be conducted. The findings of such a measurement will guide and inform policymakers as to whether any legal changes of the provision are required or any corrective action is needed. Previous studies in Bangladesh primarily focused on adolescent accessibility to smoking tobacco, but there remains a paucity of evidence on adolescents' access to SLT in Bangladesh.

SLT use has a strong cultural backdrop in South-East Asian countries but there is scant awareness available regarding its deleterious effects on health (Ebbert *et al.,* 2015). Hence, there is a need for actions that will prevent NCD risk factors by arming adolescents with adequate knowledge about chronic diseases and their risk factors. Educating school students about NCD risk factors have had a significant impact on the prevention of NCDs (Harrabi *et al.*, 2010). One study demonstrated that adolescents perceived the health risk of SLT use to be significantly associated with SLT initiation (Roditis *et al.*, 2016). Raising awareness about the risk factors of oral cancer, such as SLT use among adolescents, can encourage the adoption of protective behaviours that provide the basis for a healthy adulthood. This would immensely help the health and education sectors to plan and implement a much-needed programme for school-age children (Gamage and Jayawardana, 2017). However, once again, there is a lack of data relating to adolescent knowledge and perceptions of SLT use and its adverse effects.

Adolescents are natural partners in preventing NCDs, yet they have been overlooked in the fight against NCDs. Approximately 70% of premature deaths in adults occur due to behavioural patterns that emerged in adolescence, such as tobacco use (Pradhan *et al.,* 2013). Previous studies showed that such risk-taking behaviours manifested in mid-adolescence (14–15 years of age; Sharma *et al.,* 2010). SLT use is also regarded as a gateway drug, as using SLT in adolescence may lead to smoking and other substance misuse (Wiener, 2013; Tam et al., 2015). Therefore, the early identification of the determinants of adolescent SLT use is essential to reduce the likelihood of later substance misuse. Moreover, an understanding of the determinants of SLT use is also necessary to facilitate the interventions and policies that will strive for the eradication of adolescent SLT use.

Regarding the relationship between SLT use and oral cancer risk among Bangladeshi adults, there remain several issues that need to be addressed in the local context. Several studies in neighbouring countries, namely India and Pakistan, have established the link between SLT and oral cancer. However, studies from Sweden do not support the causal relationship of their traditional SLT, called 'Snus', and oral cancer (IARC, 2007; Boffeta *et al*. 2008; Lee and Hamling, 2009). Moreover, previous studies from the United States have suggested a much lower risk of oral cancer from SLT use compared with smoked tobacco. In particular, West Virginia in the United States had the highest prevalence of SLT use, but the incidence of oral cancer in this state was below the national average (Bouquot and Meckstroth, 2009). Therefore, the generalisability of much of the published research on this issue to another country is problematic. Also, the absence of an established relationship between SLT and oral cancer in industrialised countries has led to a debate on the benefits of using SLT as a tobacco harm reduction method and cheaper alternative to smoking cigarettes (Rodu and Goldshall, 2006).

SLT products differ considerably in their concentrations of nicotine and volatile and non-volatile nitrosamines, including tobacco-specific nitrosamines (TSNAs), toxic metals and other compounds (NCI and CDC, 2014). Notably, the level of TSNAs in SLT products consumed in different countries varies and can differ by as much as 400-fold (Stanfill *et al*., 2011). Also, the relative risk (RR) of developing oral cancer from SLT use varies substantially among products, regions, dosages and the duration of use (IARC, 2007). The cancer-producing activity of SLT products also varies significantly due to the method of processing and variations in temperature, fermentation and curing (fuel curing, air curing or smoke curing). This further hinders the comparability of the results of various studies evaluating the health effects of SLT use (Boffetta *et al.*, 2008).

Although Bangladesh has one of the highest SLT prevalence rates and the third-highest oral cancer incidence rate in the world, there is no epidemiological data that is related to oral cancer risk factors for this context. Conflicting results between the studies from industrialised countries and developing countries suggest there is a need for a new investigation that would explore the relationship between SLT use and oral cancer among Bangladeshi adults. The variations of chemical components in SLT products across different regions have most likely contributed to this discrepancy. The recent chemical characterisation of 31 brands of Bangladeshi SLT products from Bangladesh (see table 5, p.39 to see the most common type of SLT products used in Bangladesh) revealed that the chemical characterisation of contained significantly higher ($p < .05$) levels of TSNAs compared with SLT brands from the United States and were higher on average than the levels observed in brands in other countries of South Asia (Nasrin *et al.*, 2019). Thus, further investigation is necessary to characterise oral cancer with various SLT products used in Bangladesh.

Bangladesh faces the double burden of SLT use and oral cancer-related deaths. To prevent future uptake of this deadly habit, it is essential to examine adolescent SLT use and its associated factors and then use this research to inform interventions that seek to prevent future uptake of the SLT habit. This study is important as it will add to the growing body of literature regarding SLT use by adolescents and assist policy makers and other public health professionals to develop efficacious policies and interventions that can prevent and reduce SLT use among adolescents. Additionally, to reduce the current burden of SLT-related harm, it is essential to generate local evidence of oral cancer that is associated with SLT use in Bangladesh. This will inform policy provision, contribute towards etiological research on SLT use and oral cancer in Bangladesh, which is currently lacking, and address the discrepancy that exists between the research findings from developing and developed countries. A detailed framework of the relationship between the two studies is provided in Chapter 3, p 166.

1.6 Aim and objectives

This PhD aims to examine the factors contributing to adolescent SLT use in Bangladesh and the role of SLT in oral carcinogenesis among Bangladeshi adults. Thus, the study findings will inform interventions and policy in order to reduce the current and future burden of SLT-related harm in Bangladesh.

Two studies were carried out to achieve this aim, as described below.

A school-based cross-sectional study was conducted in two rural schools in Bangladesh with the following objectives:

- To investigate current practice and the pattern of SLT use among adolescents aged 13–15 years.
- To determine their knowledge and perception of the adverse effects of SLT use.
- To determine the predictors of current SLT use among adolescents aged 13–15 from rural schools in Bangladesh.
-

A hospital-based case-control study was carried out according to the following objectives:

- To assess the risk of oral cancer associated with SLT use in a sample of Bangladeshi adults.
- To estimate the number of oral cancer cases attributed to SLT use in Bangladesh from the odds ratio derived from both the case-control study and national prevalence of SLT use.
- To evaluate the role of other known (i.e. smoking and alcohol consumption) or putative (oral health indicators, family history of cancer) risk factors for oral cancer in the study population.

1.7 Thesis structure

The overall structure of the thesis takes the form of five chapters. Chapter 1 contextualises the research by providing background information on the SLT pandemic and its associated burden, establishes the problem statements and presents the research gaps. Chapter 2 is divided into two sections. The first section provides a review of studies on adolescent SLT use and its related factors, then lays out the theoretical dimensions of the school survey and outlines how these concepts support the objectives outlined above. The second part focuses on the studies of oral cancer epidemiology and risk factors, as well as their possible relationship with SLT use, followed by a theoretical overview of oral cancer risk factors. Chapter 3 presents the methods that guided the research and analyses. Chapter 4 draws together the research findings, which are described according to the research objectives that guided this study. Chapter 5 provides a brief summary and critique of the findings in relation to the existing research, presents the strengths and limitations of the methods used to achieve the research objectives, discusses the implications and recommendations of the findings for public health policy, practice and future research and offers an overall conclusion of the research.

Chapter II: Literature review

The overall aim of this literature review is to provide a comprehensive background for understanding current knowledge related to adolescent SLT use. and oral cancer risk factors among adults and highlighting the significance of new research. Therefore, a narrative literature review approach was adopted to summarize what has been previously published in the related field in order to identify gaps of research and knowledge. According to Green, Johnson and Adams, (2006) narrative reviews can inspire research ideas by identifying gaps or inconsistencies in a body of knowledge, thus helping researchers to determine research questions or formulate hypotheses.

Another literature review approach that could be considered for use is systematic review. According to Moher *et al., (*2009) "A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarize the results of the included studies." Some of the key strengths of systematic review are – focused on a unique enquiry, transparency in retrieving articles for literature review, objective and quantitative, summary, and inferences based on evidence (Collins and Fauser, 2005). However, the applicability of systematic review regarding health behaviour maintenance is limited with regard to reporting, methodology and thematic coverage (Loef and Walach, 2015). In contrast to systematic review, narrative review can address one or more research question and the selection criteria for inclusion of the articles may not be specified explicitly. Subjectivity in study selection is the main weakness ascribed to narrative review that potentially leads to biases (Yuan and Hunt, 2009). Additionally, doing two separate systematic reviews for two separate research questions would be challenging as present study used two separate research methods to address the research questions. However, to improve the quality and rigour of this narrative review, techniques used in article selection and bibliographic search strategy in systematic reviews were adopted.

To better understand what has previously been investigated, and to set the stage for the present study, the literature review chapter is arranged in two separate sections: (1) a review of the factors related to adolescent SLT use and the theoretical overview of adolescent SLT use; and (2) a review of the literatures on oral cancer epidemiology, aetiology of oral cancer, biochemical and epidemiological evidences of SLT use and oral carcinogenicity, and lastly theoretical overview of oral cancer risk factors.

2.1 A review of the factors associated with adolescent smokeless tobacco use

2.1.1 Introduction

The development of adolescent SLT use is a dynamic process that starts from an early trial and moves to repetitive use, becoming a regular user and lastly tobacco dependency. Understanding the key factors that either prohibit this progress along with continued use is critical to prevent SLT use. Not every adolescent that tries tobacco products at an early age becomes regular users. Perhaps different factors play a critical role in different points in the life course. For instance, early use of tobacco products is likely to be influenced by social and environmental factors, whereas interpersonal factors contribute to the continuation of tobacco use and tobacco dependence in later life stages (Bellatorre *et al.*, 2016; Hussain *et al.*, 2017). However, the relationship of these factors with adolescent SLT use is not yet fully understood (Smith *et al.*, 2015).

The next sub-sections include search strategy and article selection process, critical review of the selected articles and conclusion about the overall findings of the review.

2.1.2 Search strategy and article selection

An electronic search was carried out in PubMed, ProQuest and Google scholar data bases in 2018. Searches utilised MeSH (Medical Subject Headings) terms and combinations of the following words and their appropriate iterations: adolescent. young, school student, smokeless tobacco, chewing tobacco, betel quid, tobacco, factors, predictors, knowledge, awareness and perception.

The author was independently involved in article searching, screening and selection process. Main titles were read to identify potential articles related to the topic. Initially all the articles that appeared to present SLT/chewing tobacco to participants of adolescent, young and school students were included. later abstracts were reviewed, and articles related to adolescent SLT use and related factors were retained and those did not match the inclusion criteria were excluded. The author had also scanned the eligible articles reference list to identify the additional articles. The final included articles were cross-checked by the PhD supervisors.

2.1.2.1 Study inclusion criteria

- Cross-sectional study design
- Reviews considered school-going adolescents.
- Studies which reported the SLT prevalence and at least one associated factor were included in the review.

- Only studies published in English were included.
- No year limits.

2.1.2.2 Study exclusion criteria

- Studies conducted other than school adolescents.
- Studies published in other language.
- Studies that solely focused on other forms of tobacco rather than SLT.
- Editorial comments, conference proceeding, and qualitative studies were excluded from the review.

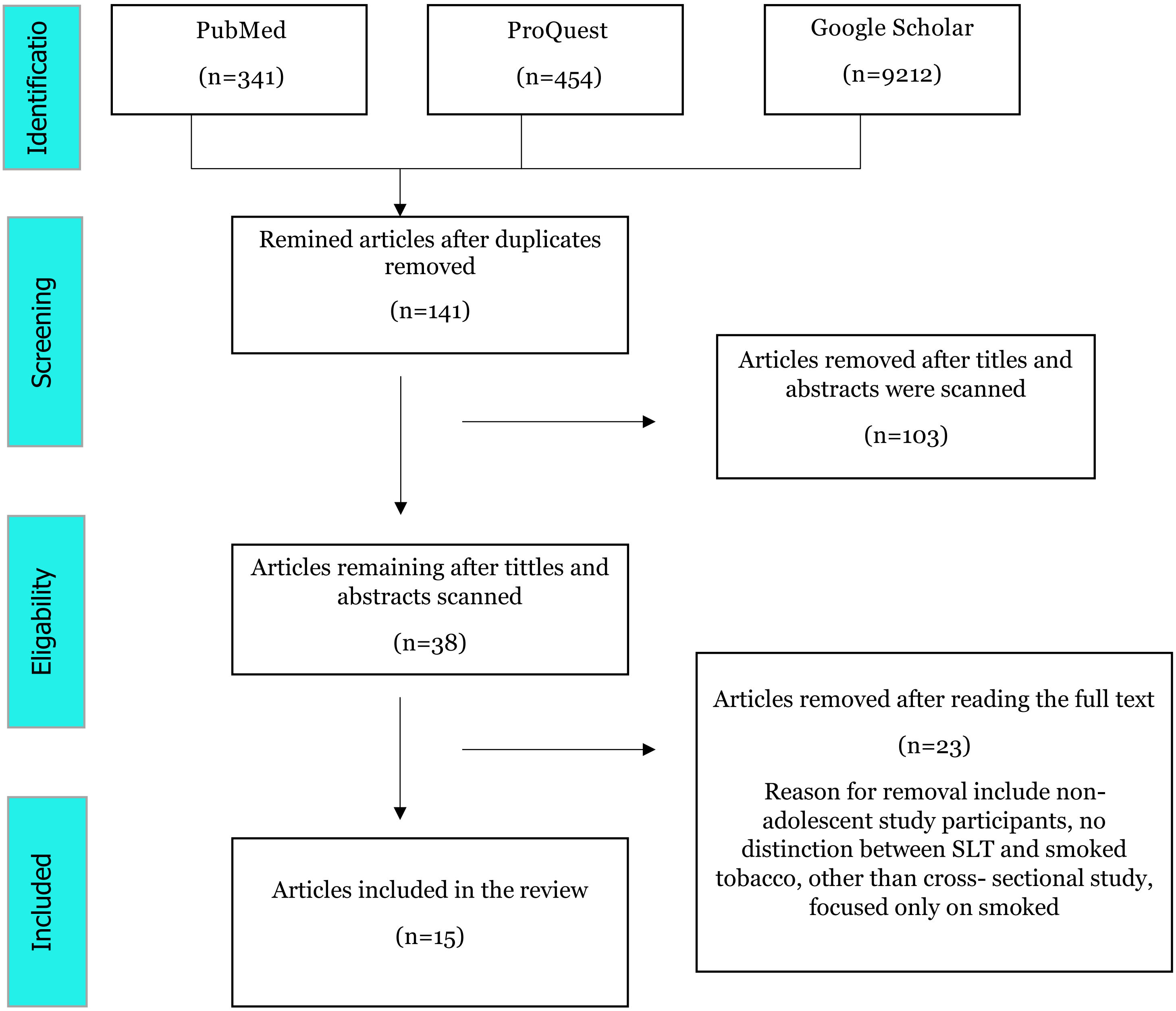


Figure 3a: Flow chart of articles selection process for the review

2.1.3 Review of the articles

2.1.3.1 Socio-demographic factors

The included studies explored the association between the independent variables (socio-demographic factors namely age, gender, parenteral socio-economic status (SES), race and ethnicity, and area of residence (urban/rural)) with SLT use (dependent variable).

Age

Age was consistently associated with both SLT initiation and continuation. Most SLT users began the habit in adolescence and the prevalence increases with age. A study based on the US National Youth Tobacco Survey data- 2011 (18 866 students from 178 middle and high schools) revealed that the prevalence of current SLT use increased with age and was lowest among respondents aged 9 to 11 years (2.2%) and highest among those aged 18 years (10.8%; Agaku *et al.,* 2013). Similar proposition was made by Hawkins, Bach and Baum (2018). The study was based on the data on 499,381 adolescents age 14-18 years from 36 US states in the Youth Risk Behaviour Surveys (1999-2013). The study findings showed that tobacco use increased with age, as the odds of SLT use nearly doubled from ages 14 to 18 years.

Not all studies reported similar findings. Contrary findings were reported in a previous study based on GYTS data from Congo. The survey result showed that younger respondents had higher rates of SLT use, with almost one-third of adolescents started using SLT before the age of 11 years (33.0%) compared with 12.8% at 16 years. Older age showed inverse association with adolescent SLT use and was statistically significant. However, the association lost its significance after considering other variables (Rudatsikira *et al.,* 2010).

Most studies found that the age of onset for adolescent SLT use was between 10 and 13 years (Rudatisikira *et al.*, 2010; Agaku *et al.*, 2013; Kumar *et al.*, 2014; Veeranki *et al.*, 2015; Chatterjee *et al.*, 2016; Hussain *et al.*, 2017). However, no research has been conducted to examine the age pattern of adolescent SLT use in Bangladesh. A recent GYTS survey report showed that more than half (56.4%) of Bangladeshi adolescents started using tobacco at the age of 12–13 years, but this evidence is not exclusive to SLT use, as it included both SLT and smoked tobacco (WHO, 2015).

Gender

Historically the prevalence of SLT was higher among boys than girls. However, this trend differs geographically. Most studies from the US found that boys are more likely to use SLT than girls (Agaku *et al.*, 2013; Wiener, 2013). A similar trend was observed in

South-Asia. A recent study conducted in Bhutan, found that boys were three times more likely to be current SLT users than girls (Rinchen *et al.,* 2018). Studies from India, Nepal and Pakistan reached similar conclusions (Bhaskar *et al.*, 2016; Chatterjee *et al.*, 2016; Hussain *et al.*, 2017).

In contrast, studies from the African region showed a mixed result. Contrary to South-Asia, the study from South Africa found that female adolescents were predominantly SLT users and males were predominantly cigarette smokers (Ranatao and Olalekan, 2012). Additionally, studies based on GYTS data for Sudan and Congo did not find any significant gender difference in adolescent SLT use (Rudatsikira *et al.*, 2010; Atari, 2014).

In Bangladesh, women are the dominant users of SLT products than men. However, in case of adolescent, it followed the opposite trend, as the recent GYTS report showed that 5.9% of Bangladeshi boys were current SLT users compared to only 2% of girls (WHO, 2015).

Socio-economic status

Past studies have suggested that lower SES (Socio-economic status) is associated with increased tobacco use among adults. However, the association between SES and adolescent SLT use differs from what we find in adults (Lauterstein *et al.*, 2014; Wilkinson *et al.*, 2015). One of the key reasons for this difference would be the construct of SES itself, as SES is conceptualised and measured differently for adults and adolescents. Conventionally, SES status of the adolescent is measured using two main factors-education and occupation of the parents, which capture the structural position of the adolescents in the socio-economic hierarchy (Viner *et al.*, 2012).

Higher levels of parental socioeconomic variables, such as education has often been found to be inversely related to SLT status in adolescents—for example, in a large longitudinal study, Patricia *et al.,* (2016) investigated current SLT use among adolescents and its relationship with parenteral education. The findings indicated that adolescents with at least one parent who completed high school were less likely to be current SLT users compared with those with both parents who had not completed high school. However, some studies suggested father's education status is one of the key predictors. A school survey among Ghanaian adolescents found that adolescents whose father had low education were two times more likely to be SLT users compared to those whose father had tertiary education, OR = 2.3, 95% CI [1.0, 5.0], but use was not affected by the mother's education level (Doku *et al.,* 2010).

In contrast, Ranatao and Ayo-Yusuf (2012) found that a mother's educational attainment was a strong predictor of adolescent SLT use. These mixed results are found throughout the literature. A large cohort study with 1,352 Mexican adolescents reported the opposite: adolescents whose parents had higher educational attainment were two times more likely to be current SLT users compared to those whose parents had lower educational attainment (Wilkinson *et al*., 2015). Additionally, a recent review based on US national surveys exhibited that adolescent SLT use did not appear to be correlated with the level of parental education (Lauterstein *et al.,* 2014). Given these mixed results concerning the relationship between parenteral education and adolescent SLT use, further investigation is needed.

Race and ethnicity

It might be conceptualised that the degree to which individual's from various ethnic backgrounds identify would be related to the adoption of certain health behaviour including tobacco use. Several studies had identified multiple pathways through which race and ethnicity may influence adolescent tobacco use (Lee *et al.*, 2015; Choi *et al.*, 2018; Park *et al.*, 2018). An extensive national-level survey among students in grade six to 12 in the United States showed that white adolescents used chewing tobacco more frequently, whereas cigarette smoking was more common among African American adolescents and e-cigarettes and hookah among Hispanic adolescents (Choi *et al.*, 2018). Similar conclusion was made by Park *et al.*, (2018) and Lee *et al.,* (2015), they found that African American and Hispanics are less likely to use SLT compared with non-Hispanic Whites.

It is possible that a strong ethnic identity plays a key role in adolescent tobacco use behaviour. For instance, earlier studies found that a strong ethnic identity was associated with a lower risk of tobacco use among adolescents in several ethnic or racial minority group, including African Americans and Hispanics (Brook *et al.*, 2007). However, the mechanism behind this association is still unclear and complicated, as major predictors of adolescent tobacco use, such as low SES, unemployment and low level of education, are more prevalent among Black minorities.

Place of residence

Several studies have examined the effect of geographical differences in adolescent tobacco use. In general, past studies exploring rural and urban differences in adolescent SLT use behaviours consistently argued that greater SLT use was seen among rural adolescents. A cross-sectional study of 4332 adolescents in 8th to 10th grades in 25 urban and 24 rural secondary schools in Enugu, Nigeria found that higher SLT use among rural adolescents (31.1%) vs those living in urban areas (22.7%). Moreover, dual use of smoked tobacco and SLT was more than double in rural areas (3.1%) compared to urban areas (1.4%; Itanyi *et al.*, 2018).

Studies from indistrial countries also found a similar difference in adolescent SLT use. A recent study based on national youth survey data from the United States found that adolescent SLT use in rural areas was 6.98% compared to only 2.98% in urban areas

(Pesko, *et al.*, 2017). Similarly, Warren, Smalley and Barefoot (2017) argued that rural adolescents are two times more likely to be current SLT users compared to their urban peers. The characteristics of rural areas such as lower-income, lower educational attainment and easy access to SLT products have been identified as potential contributors to these disparities. However, it is unclear what percentage of this difference can be explained by these factors (Pesko *et al.*, 2017). Another explanation of this difference between rural and urban areas could be because of a higher proportion of older adolescents living in rural areas compared to urban areas (Itanyi *et al.*, 2018).

As mentioned, data associated with adolescent SLT use in Bangladesh is limited. However, studies among Bangladeshi adults showed that SLT use is more prevalent in rural areas of Bangladesh compared to urban areas (Nargis *et al.*, 2015; Huque *et al.*, 2017). A study to establish adolescent SLT use disparities in rural and urban areas is yet to come. Nevertheless, given the socio-economic condition of the country and evidence from other developing countries, it is expected that the disparities of adolescent SLT use based on area of residence is expected to be substantial.

2.1.3.2 Environmental factors

Several environmental factors that have the potential to influence initiation and maintenance of SLT use by adolescents have been focus of many investigations and early studies demonstrated the key role of environmental factors. Two of the key environmental factors that were stdued extensively were: access and availability of SLT products and tobacco advertisement. However, interpretation of these study findings were challenging because of inconsistencies in the dependent variable (SLT use status, SLT initiation, and attitude), the different combinations of independent variables and the variety of analytical approaches that has been used.

Access and availability

Many studies have investigated the relationship between the access and availability of tobacco and adolescent smoking. However, few studies have investigated the access and availability of SLT and their effect on adolescent SLT use. According to Williams *et al.*, (2018), Adolescents' access to tobacco products can be categorised into two main sources: formal (commercial retailers) and informal sources (social sources). Social sources include family members, friends and relatives.

A cross-sectional study of 172 adolescents from grade eight, nine and ten in India revealed that the availability, accessibility and affordability of tobacco products are key contributors to the level of adolescent tobacco use. They found over 90% adolescent was not refused to purchase tobacco products because of their age (Patel, Kassim and Croucher, 2012). However, this information was not exclusive to SLT access rather included both smoking and SLT.

Poor implementation of Tobacco Control Law (TCA) resulted easy access of SLT to the adolescents. A large cross-sectional survey among 1,373 high school students and 436 tobacco vendors in India showed that point of sale tobacco control policies compliance was low but when it was applied, it was associated with a lower risk of current SLT use, OR = 0.40, 95% CI [0.21, 0.77] (Mistry *et al.,* 2018).

The availability of SLT products near schools also increased the risk of adolescent SLT use. A survey among 1,918 students from grades seven, eight and nine showed that the ability to buy tobacco products within 100 yards of the school was associated with an 11-fold increase in tobacco use among adolescents (Chatterjee *et al.,* 2016). Hussain *et al.*, (2017) made a similar point in their recent survey among school students in Karachi, Pakistan. They found that the availability of SLT at the school canteen and outside the school with street hawkers played a substantial role in adolescent SLT use. Adolescents were nearly four times more likely to be current users if SLT was available in or outside the school with street hawkers, OR = 3.65, 95% CI [2.8, 4.73] (Hussain *et al.*, 2017).

Similar to commercial sources, social sources also play a significant role in adolescent SLT use. In early adolescence, informal or social sources have the greatest impact, whereas in late adolescence, formal or commercial sources and friends are the primary sources of tobacco for adolescents (Warren *et al.*, 2015). A large school survey among 2000 middle and high school students from the US found that nearly 68% of the study participants obtained SLT from social sources, whereas 26.2% bought it from commercial sources (Kaestle,2009). Another study from Finland drew a similar conclusion, as 84% of the study participants acquired SLT from friends or acquaintances (Huhtala *et al.*, 2006).

Poor implementation and inefficiency of current tobacco control laws in certain countries are making SLT easily accessible to adolescents. As mentioned, Bangladesh has recently addressed this issue. In 2013, Bangladesh amended its tobacco control law and banned the sale of any form of tobacco product to and by minors (WHO, 2013b). However, the effectiveness of this new law amendment has yet to be assessed.

Tobacco advertisements

Several studies have established the role of tobacco advertisement and adolescent SLT use. The evidences are consistent and robust that advertising and promotional activities of the tobacco companies lead to adolescent SLT use, including initiation as well as the continuation of use. Advertisements in mass media are powerful tool and can influence behavioural change through creating a positive image in one's mind. The influence on behaviour by media is created in two ways: frequency of exposure and content of the exposure (Sardana *et al.*, 2015).

A longitudinal survey among 3,376 US adolescents found that adolescents who can identify a SLT brand were two to three times more likely to use SLT and use on 20 or more occasions compared to those who did not identify any SLT brand (Timberlake, 2016). An extensive population-based study in the United States, also known as the PATH study (Population Assessment of Tobacco and Health study), included 10,989 study participants. The findings showed that the receptivity of tobacco advertising among adolescents aged 12–14 years was 44% and receptivity to the SLT product advertising was associated with progression to current SLT use among those who have never used SLT (Pierce *et al.,* 2018).

Further study among US adolescents found that students were three times more likely to use SLT if they were exposed to pro-tobacco advertisements at retail stores and on the internet, OR = 1.6, 95% CI [1.24, 2.09], compared with those who did not (Agaku *et al.*, 2014). A broadly similar point was made by Rudatsikira *et al.*, (2010) in their study based on GYTS 2006 data from India. The results indicated that adolescents who reported seeing tobacco advertisements on print and digital media were nearly two times more likely to be current SLT users compared to who did not, OR = 1.95, 95% CI [1.34, 3.08]. In Bangladesh, the advertising of SLT products is banned in both print and electronic media (Huque *et al.*, 2017). However, the usefulness of the current law is yet to be confirmed.

2.1.3.3 Social factors

Social factors like, SLT products used by either of the parents and friends are the common and significant contributors towards adolescent SLT use. Previous studies had proposed these two factors as strong determinants of adolescent SLT use.

Parental use

The impact of parental SLT use has been studied in a wide range of contexts in a large number of studies with a range of outcomes. To date several studies found that exposure to parental SLT use is predictive of onset and continuation of SLT use by adolescents.

A survey among US adolescents showed that adolescents whose parents were SLT users were three times more likely to be current SLT users compared to those with non-user parents, OR = 3.32, 95% CI [2.23, 4.95] (Agaku *et al.,* 2013). A similar conclusion was made by Hussain *et al.,* (2017) in their survey among 2,140 adolescents from secondary schools in Karachi, Pakistan. Their findings showed that adolescents who had one parent as a current SLT user were two times more likely to use SLT as well, OR = 2.16, 95% CI [1.73, 2.65] and for both parents using SLT, OR = 2.50, 95% CI [1.44, 4.34]. Similarly, a large cross-sectional study among 4,277 Sudanese students (aged 11–17 years) found that Parental SLT use was directly associated with adolescents' ever (OR 1.77, 95% CI 1.30 to 2.41) and current (OR 1.84, 95% CI 1.17 to 2.90) SLT use (El-Amin *et al.,* 2011).

A large survey among 2232 Swedish adolescents from the fifth grade looked at whether gender of the parents has any influences on adolescent SLT use. The study findings showed that paternal use of SLT was associated with an increased risk of SLT use among Swedish boys. However, the risk was higher if mother is a SLT user than father. Adolescents were four times more likely to use SLT if mother uses the SLT and three times more likely to use SLT products if father uses SLT (Rosendahl, *et al.,* 2003).

The overwhelming evidence of the positive association between parental and adolescent SLT use is based on several factors. First, adolescents may see their parents as their role models and try to imitate their habits, a concept supported by the theory of planned behaviour (Alves *et al.*, 2017). Other authors suggested a permissive family atmosphere, dysfunctional family, stressors and shared personality traits may better explain adolescent tobacco use (Pattanayak *et al.*, 2011). Further, experts have suggested adolescents have easy access to SLT when a parent also uses, which is seen as socially acceptable in some cultures and plays a critical role in early use Irrespective of the motive of this association, study findings are consistent about the positive relationship between adolescent SLT use and parental use of SLT.

Peer pressure

Peer pressure is one of the strongest predictors of adolescent SLT initiation, continuation and quitting behaviour and has been studied extensively (El-Amin *et al.,* 2011; Agaku *et al.*, 2013; Shrivastava *et al.,* 2015; Malhotra *et al.*, 2016; Sharma *et al.*, 2017; Hussain *et al.*, 2017). The mechanism of peer influence is most often postulated in social learnings (Bandura, 1995), whereby adolescents learn about tobacco use by observing their friends use tobacco products and are reinforced by perceiving the advantages. For example, adolescents assume using tobacco will help them gain acceptance from peers or establish a positive social identity.

Another mechanism is the direct pressure from peers to use tobacco. A recent cross-sectional study among 2,140 adolescents from secondary schools in Karachi, Pakistan found that the current use of SLT by adolescents was significantly associated with peer SLT use (Hussain *et al.*, 2017). The findings indicated that adolescents whose friends used SLT were six times more likely to be current SLT users compared to those with non-user friends and the association remained significant after adjusting for parental use, teacher SLT use status and other individual and environmental factors, OR = 6.79, 95% CI [4.67, 9.87] (Hussain *et al.*, 2017).

Previous study result showed as peer influence as the frequent reason for SLT initiation. A cross-sectional survey among 1006 school students from India found that 76% students initiated SLT because of peer influence whereas only 14% students initiated SLT because of self-interest (Shrivastava *et al.*, 2015). This influence seemed to be higher when adolescents resides in the same setting. A cross-sectional study among 378 Bhutanese adolescents found that the current prevalence of tobacco use was 36.7% among adolescents with friends using tobacco products compared to 13.5% those without a friend using tobacco products, OR = 3.71, 95% CI [1.66, 8.28] and interestingly 80% of the student participants resides in the school hostel and the likelihood of getting influenced by their peers was more than that of their parents or siblings (Rinchen, Taneepanichskul and Dawa, 2018).

Using SLT products by the peers had shown significant influence on adolescent SLT use. However, other form of tobacco use such as cigarette smoking by peers is not associated with current SLT use by adolescent. The US study based on data from the 2011 National Youth Tobacco Survey data found that, adolescents are nine times more likely to use SLT if their peer also uses SLT (aOR: 9.56; 95% CI: 7.14–12.80). However, cigarette smoking by either peers or household members was not significantly associated with current SLT use (Agaku *et al.,* 2013). Contrasting, a survey among 4277 Sudanese school-going adolescents (aged 11–17 years) from 23 schools found that tobacco smoking in friends was positively associated with adolescents ever SLT use (local SLT product) (OR 1.81, 95% CI 1.41 to 2.33) and current dipping (OR 3.33, 95% CI 2.20 to 5.05). However, the study failed to measure the effects of peer's SLT use (only smoking was measured) on adolescent SLT use (El-Amin et al., 2011). Similiarly, previous study from Congo reported that friends smoking status is a strong predictor of adolescent SLT use. Adolescents were two times more likely to use SLT if they have friends who smokes (Rudatsikira, Muula and Siziya, 2010).

As discussed above, there is a paucity of data related to adolescent SLT use in Bangladesh. However, GYTS (2007) data indicated that a friend's tobacco use was associated with a three-fold increased risk of adolescent tobacco use, OR = 3.46, 95% CI [2.37, 5.05] (Kabir *et al.*, 2015). However, this information is not exclusive to SLT use.

2.1.3.4 Personal factor (knowledge and awareness)

Knowledge about the consequences of tobacco use is viewed as a moderator of adolescents' decisions to use tobacco (Rosendahl *et al.*, 2005). Knowledge and awareness of the health effects of tobacco use are expected to change the attitude and expectation towards the substance use and become a part of a distal determinants of tobacco use (Conrad *et al.*, 1992; Flay *et al.*, 1999).

There is a great deal of controversy whether knowledge is a good predictor of adolescent tobacco use. Also, there is a paucity of data related to adolescent knowledge and perception of SLT use-related health risks. Of the studies available, most either focused on the knowledge and perception of smoking tobacco or mixed-use and rarely on adolescent knowledge and perception of SLT use and its related harms. Careful understanding of adolescent knowledge and beliefs about SLT use is essential for effective prevention efforts.

Studies have indicated that most adolescents know SLT use is bad for their health. A cross-sectional survey among 1,514 Nepalese adolescents found that students who did not know the harmful effects of tobacco were three times more likely to be ever tobacco users compared to those had a good knowledge, OR = 3.37, 95% CI [2.53, 4.50] (Bhaskar *et al.*, 2016). However, this information is not exclusive to SLT use rather focused on overall tobacco use. Similar finding was reported by Singh *et al.*, (2015) and Goyal, (2016) and both studies looked at overall tobacco use rather than SLT use.

A large cross-sectional study among two thousand school children aged between 10 and 15 years from India looked at exclusively adolescent SLT use. The study found that over 70% of children believed that Ghutka (commonly use SLT in India) is a bad habit, but half the study population were not aware of the side effects; 30% of children believed that it is not a bad habit and has no side effects (Metgud *et al.,* 2018). However, in this study only one item was considered to measure student's knowledge related to Ghutka use. Also, no analysis was conducted to see how knowledge was associated with the Ghutka use.

Previous studies reported that adolescent had adequate knowledge related to harmful effects of SLT use. However, A number of studies reported misconception about the relative harm of SLT compared to smoked tobacco is widespread. A study among 252 US rural adolescents aged 12–17 years reported that the use of SLT has strong cultural significance and is perceived as a safer alternative to cigarettes (Walker *et al.*, 2018). The extensive campaign against smoking and little attention regarding SLT use may have contributed to the favourable perception towards SLT use. In another study based on data from the US Youth Tobacco Survey among grade 6 to 12 students argued that over 20% of adolescents thought SLT was less harmful compared to cigarettes (Randolph, 2017). This view is supported by Persoskie *et al.*, (2017), who found that nearly 30% of adolescent believe that SLT is less harmful than cigarettes.

Several studies questioned the predictability of knowledge relates to adolescent tobacco use. Early study from the US found that the belief that using SLT can cause cancer was held by nearly (97%) adolescents in the study. However, this belief had no significant effect on the likelihood of trying or regularly using SLT (Tomar, Gary and Giovani, 1998). Similarly, a cross-sectional study among 2581 Swedish adolescents found that a high level of knowledge of the risks associated with SLT use is not a predictor of future nonuse or of a shift to SLT rather than cigarettes (Rosendhal *et al.,* 2005). Also, a cross-sectional study from the United States. Horn *et al., (*2000) argued that a lack of knowledge about tobacco was not a significant predictor among exclusive smokers or SLT users but was a significant predictor among conjoint users, OR = 1.39 (Horn *et al.*, 2000). Yet, it is well documented that differences exist in knowledge and attitudes regarding SLT between users and non-users (Goebel *et al.*, 2000; Rose, Chadha and Bhutia, 2016).

Table 8: Summary of past studies related to factors associated with adolescent smokeless tobacco use

Author	Country	Sample size (male/ female)	Prv. SLT (%)	Factors associated with SLT use	OR (95% CI)
Rudatsikira *et al.*, (2010)	Republic of Congo	3,034 (1,517/1,517)	18% (current)	Cigarette smoking	6.64 (4.84-9.14)
				Parents smokers	1.98 (1.51-2.59)
				Friends smokers	1.82 (1.41-2.69)
				Seen tobacco ad on TV, billboards	1.95 (1.34-3.08)
				belief that tobacco use is harmful	0.60 (0.46-0.78)
Chatterjee *et al.*, (2016)	India	1,918 (949/969)	5% (current)	Male students	2.5 (1.0-6.1)
				Use any form of tobacco have more friends	2.8 (1.4-5.6)
				Availability of tobacco product within 100 yards of the school	10.8 (3.0-38.6)
Rinchen and Taneepanichskul (2018)	Bhutan	378 (178/200)	11.10% (current)	Male	3.22 (1.76-5.91)
				Tobacco use by siblings	3.88 (1.06-14.19)
				Tobacco use by friends	3.71 (1.66–8.28)
				Ever having tried alcohol	8.28 (4.41–15.56)
Wilkinson *et al.*, (2015)	Mexico	1,087 (538/559)	5.7% (ever)	being male	1.86 (1.02-3.41)
				social status	0.78 (0.64-0.93)
				higher parental education	2.01 (1.03-3.93)
Veeranki *et al.*, (2015)	Madagascar	1,184 (535/649)	7% (Current)	Smoking peers (male)	7.36 (2.20 -24.66)
				Exposure to second-hand smoking at home (female)	12.40 (3.92-39.23)
Bhaskar *et al.*, (2016)	Nepal	1,540 (526/1,114)	9.2% (ever Khaini) and 8.4% (ever Gutka/panma sala)	Male students	3.2 (1.4–5.2)
				Janajati ethnicity	5.41 (2.98–7.63)
				Family member using tobacco	20.16 (1.93–210.3)
				Friends using tobacco	3.78 (1.93–17.85)
				Knowledge about harmful effect of tobacco use (no knowledge)	6.17 (0.44–84.92) Continued

Author	Country	Sample size (male/female)	Prevalence of SLT (%)	Factors associated with SLT use	OR (95%CI)
Hussain *et al*., (2017)	Pakistan	2,140 (1,262/878)	42.6% (current)	Male	1.38 (1.05–1.83)
				Government school	2.06 (1.49–2.85)
				Weekly pocket money	1.51 (1.03–2.22)
				Co-education school	2.88 (1.89–4.40)
				Boys school	2.00 (1.27–3.14)
				Peers use (most of the peers)	3.02 (2.23–4.09)
				Parents (any of them use it)	1.52 (1.19–1.94)
				if closest friend offers it	4.47 (3.10–6.44)
				SLT available outside the school	3.65 (2.82–4.73)
Agaku *et al*., (2013)	United States	18,866 (9,621/9,245)	5.6% (current)	Perception of all tobacco products	0.55 (0.38–0.79)
				Peer use	9.56 (7.14–12.80)
				Households SLT use	3.32 (2.23–4.95)
Smith *et al*., (2014)	United States	938 (452/486)	9% (ever)	Female	0.26 (0.14-0.47)
				Government school	3.83 (1.31-11.15)
				Peer approval scale	1.14 (1.08-1.20)
El-Amin *et al*., (2011)	Sudan	4,277 (2,270/1,740)	3.5% (current)	Parents SLT use	2.21 (1.47-3.34)
				Friends smoking	3.48 (2.36-5.14)
				Teachers SLT use	1.21 (0.81-1.81)
Lund and Scheffels (2016)	Norway	3,196 (not available)	39.5% (current daily)	Male (for dual use)	1.44 (0.77-2.70)
				Social orientation (for dual)	1.11 (0.77-1.59)
				Legal risk	1.93 (1.38–2.70)
				Last month alcohol drinking	1.06 (1.00–1.13)
Hawkins *et al*., (2018)	United states	499,381	Ranged from 2.8% -14.8%	Male	6.91 (6.49-7.36)
				Government school	6.3 (3.2-12.6)
Rozi and Akther (2007)	Pakistan	733 males	16.1% (current)	Cigarettes smoking	3.2 (1.9-5.4)
				Seen anti-tobacco advertise (no)	1.5 (1.0-2.4)
				Family history of SLT use	3.9 (2.2-6.8)

(Table included only studies that reported odds ratio)

2.1.4 Discussions of theoretical overview of adolescent smokeless tobacco use

Formative biological and social transitions occur during adolescence and extensive efforts have been made to understand the factors that impact different types of tobacco use during this critical time of development (Hahn *et al.*, 1990; Abroms *et al.*, 2005; Hedman *et al.,* 2006; Agaku *et al.,* 2014a; Wellman *et al.,* 2016; Almahdi *et al.*, 2017a). Previous studies suggested the dynamics of SLT use among adolescents may differ from smoking a cigarette (Hu *et al.,* 1997). Several behavioural theories have been used to explain SLT initiation, continuation and cessation among adolescents. For the present cross-sectional study, social cognitive theory (SCT) and the health belief model (HBM) provide the theoretical foundation. Although the HBM model was chosen to understand individual behavioural factors that affect adolescent SLT use, other factors may also be involved. Therefore, SCT was used to understand the factors not considered in the HBM, such as environmental factors. Incorporating both theories to understand health behaviour was supported in an earlier study (Rosenstock, Strecher and Becker, 1988). Both theories are discussed below in relation of their application in previous studies and their strengths and limitations.

2.1.4.1 Social cognitive theory

SCT was first developed by Albert Bandura in 1989 and has been extensively used to explain how tobacco and other substance use patterns are acquired and maintained by adolescents (Hahn *et al.*, 1990; Langlois, Petosa and Hallam, 1999; Almahdi *et al.*, 2017). SCT is one of the components of behaviourism and explains why an individual acquires and maintains certain behavioural patterns (Akers and Lee, 1996). SCT determines the motivating factors for certain health behaviours and aids in understanding these motivations, which can help in designing health interventions to promote positive behavioural changes.

SCT is comprised of a dynamic triad of three factors (personal cognitive, socio-environmental and behavioural). Four main constructs comprise personal cognitive factors: self-efficacy, collective efficacy, outcome expectancies and knowledge. Socio-environmental factors include four constructs: observational learning, social supports, normative beliefs and barriers and opportunities. Lastly, behavioural factors consist of three constructs: behavioural skills, intentions and reinforcement and punishment (Kelder, Hoelscher and Perry, 2015). All 11 constructs of SCT influence each other at certain times and no construct is considered more important than another in determining health behaviour. However, certain constructs may be more effective when looking for a certain behaviour (SLT use) among an identified population (adolescents).

Adolescence is a time of developing a self-identity; therefore, an emphasis on self-efficacy for this age group is essential when addressing a particular health behaviour. Self-efficacy is the confidence of an individual in performing or overcoming barriers to perform a certain type of behaviour (Bandura, 1989). Individuals who had a high level of internal locus control and a high level of self-efficacy have sufficient control over negative behaviours, such as tobacco using (Bandura, 1989). A previous study showed that self-efficacy is one of the strongest predictors of an adolescent's tobacco use. A review conducted with 27 prospective studies looked at 300 possible predictors of adolescents' tobacco use and found self-efficiency, self-esteem and SES of the adolescents to be the strongest predictors (Conrad, Flay and Hill, 1992). A cross-sectional study among school-going adolescents in Delhi, India found that ever using tobacco was significantly associated with low general self-efficacy (Kumar *et al.,* 2014). Studies related to predictors of adolescents' SLT use are limited. However, one study conducted among 1,878 adolescents from South Africa showed low refusal self-efficacy and depression play a vital role in the dual use of tobacco (Rantao and Ayo-Yusuf, 2012). These findings emphasise that adolescent substance use, including SLT, is associated with low general self-efficacy.

Another key construct often cited in relation to adolescent tobacco use is outcome expectancies, which is defined as the belief that a behaviour will lead to a certain outcome and, therefore, may influence behaviour (Bandura, 1989). According to Rash and Copeland (2008), outcome expectancies refer to the anticipated reinforcing and punishing consequences related to using a substance, in both the short and long-term. Outcome expectancies and behaviour may emphasise each other since expectancies reflect an individual's experience with a substance. For example, one study explored whether outcome expectancy could predict adolescent tobacco use or susceptibility using a six-month follow-up survey among an adolescent cohort of never users of tobacco products. The study result showed that the outcome expectation related to stress relief predicted ever tobacco use and susceptibility (Colvin and Mermelstein, 2010). Similar findings were reported in previous study among Norwegian adolescents that found positive outcome expectation related to stress relief or less harmfulness and positive attitude were the strongest predictors of adolescent SLT use (WIIUM and AARØ, 2011).

SCT has a reciprocally deterministic viewpoint and hypothesises that no amount of observational learning will lead to behaviour change unless the observers' environments support the new behaviours (Mcaloster, Perry, and Percel, 2015, p.159). One basic form of environmental change to modify behaviour is incentive motivation, through the provision of rewards or punishments for desired or undesired behaviours. Increasing the prices of SLT products through taxation is a less punishing form of incentive motivation which can deter adolescent SLT use (NCI and CDC, 2014). It allows immediate reward of more money to spend on other things those who choose not to purchase SLT.

Regarding observational learning, human capacity of learning new behaviour through other is central to SCT. SCT posits that adolescent tobacco use is a learned behaviour acquired through social interaction and support. The widely cited relationship between adolescents' tobacco use and their friends' (Cadmus and Ayo-Yusuf, 2018) and parents' (Rudatsikira, Muula and Siziya, 2010) tobacco use status can be seen as evidence of observational learning.

Strengths and limitations of social cognitive theory

Many researchers support the effectiveness of using SCT to explore health behaviour change (Short, James and Plotnikoff, 2012). The real value of SCT lies in its explanatory power for behaviour change, supporting the importance of self-efficacy and the existence of a wide range of empirical evidence for other SCT constructs. SCT is regarded as an evolving theory that is open to change, as Bandura's (1986) own development of SCT came from social learning theory. Despite its openness to change for improvement, several limitations must be considered when evaluating the theory. First, SCT assumes that changes in the environment will automatically lead to changes in a person's behaviour, which is not always the case (LaMorte, 2019). Second, the theory is broad reaching, so it can be difficult to operationalise. Third, SCT is highly focused on the individual, which means group elements are thought to only play a small role besides in the modelling component. Also, social, economic and political factors, also known as ecological factors, are completely ignored (LaMorte, 2019). Last, SCT has been widely used in the field of health promotion that emphasises individual and environment factors, but like other theories, applying all constructs to a single public health problem is difficult.

2.1.4.2 Health Belief Model

The HBM has been a widely used framework in health behaviour studies to describe both initiation and maintenance of health-related behaviours and interventions (Glanz, Rimer and Viswanath, 2015). The model was first developed in the 1950s by social psychologists in the United States. The model is based on the understanding that an individual will take health-related action (e.g. will not use SLT) if they feel the adverse health condition can be evaded, have a positive expectation that by accepting recommended action they will avoid the health hazard and believe they can complete the recommended action successfully (Glanz, Rimer and Viswanath, 2015).

The model has several primary concepts that assist in predicting why an individual will act to control, prevent or screen disease conditions: perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action and self-efficacy. The first four constructs were developed with the original model and last two were added as the HBM evolved.

The HBM shows the relationship between health beliefs and specific health behaviour. Based on this model, if an individual feels that they are exposed and sensitive to a situation (perceived susceptibility), are certain that the situation is likely to be dangerous and will have negative consequences (perceived severity), think that through a series of actions they can reduce the risk and effects of the situation, believe the benefits of these actions (perceived benefits) are greater than the barriers of doing the behaviour (perceived barrier), they will perform preventive behaviours to avoid the risk. Additionally, a stimulus can work as a trigger for a specific behaviour and can be considered as a guide and reason for the action (cues to action); in this sense, a person will have a sense of effectiveness and tolerability by overcoming the barriers of the specific behaviour (self-efficacy; Glanz, Rimer and Viswanath, 2015).

The HBM is a psychological model that aids in explaining and predicting health behaviour (Mohammadi *et al.,* 2017) and has been applied to the prediction of an impressively broad range of health behaviours among a wide range of populations. Two of the broad areas it has been used in are preventive health behaviour (diet and physical activity) and health risk behaviour (e.g., tobacco use). However, the HBM has yet to be applied to predict adolescent SLT use behaviour, as the majority of studies have used this model to predict only smoking behaviour. For instance, a cross-sectional study among 470 secondary school students found that positive attitude, weaker perceived barriers and cues to action were effective predictors of smoking behaviour (Mohammadi *et al.,* 2017).

The HBM was used in a tobacco-related study by Weinberger *et al.* (1981), who found that certain types of attitude and beliefs can distinguish between different levels of tobacco use behaviour (past, moderate and heavy users) and quit tobacco habits. The researchers highlighted that users must see themselves susceptible to adverse effects of tobacco use in addition to believing that using tobacco products is a health risk before change occurs. Concerning SLT use, Tareg *et al.*, (2015) assessed individuals' beliefs of the health risk of betel nut chewing among the population of Yap, Micronesia using the

HBM as a basis for their questionnaire design. Ghajari *et al.* (2017) examined the predictors of smoking among high school boys using HBM constructs by focusing on the attitude and beliefs of individuals. A previous review by Mantler (2013) used the HBM framework to assess youth's perception of addiction and health risk associated with smoking, finding that youths considered the perceived barriers to quitting as more relevant than the benefits of quitting but when they decided to quit, this scenario was shifted, and they believed the benefits to be more relevant.

Strengths and limitations of the health belief model

The HBM is a useful framework to understand health behaviour. In general, the constructs are seen as independent predictors of health risk behaviour (Orji, Vassileva and Mandryk, 2012). Despite the success of the HBM in predicting a range of health risk behaviours, previous research claimed that HBM constructs were inadequate predictors (Norman and Brain, 2005). Some of the major limitations of the HBM are the low predictive capabilities of the constructs, their small effect size and a lack of clear guidelines for combining the constructs and understanding the relationship between them. According to Orji, Vassileva and Mandryk (2012), the constructs of the HBM can only predict approximately 20% of the variance in health behaviour. Yarbrough and Barden (2001) concluded in their review that the application of the HBM is inconsistent in explaining breast screening behaviour and only explained 47% of the observed variance in screening behaviour when SES was included; otherwise, the predictive power of the HBM ranged from 15% to 27%. Even the extent of the perceived threat as an effective behavioural motivator has been questioned in the context of adolescents' behaviour (Finfgeld *et al.*, 2003).

2.1.5 Overall summary

The review on adolescent SLT use found that age, gender, parental education status, ethnicity, area of residence, easy accessibility and availability of SLT, tobacco advertisement, parental use and peer pressure are the key factors associated with adolescent SLT use. The majority of the studies agreed that adolescent SLT use increases with age. Studies from the South-Asia region and the US found that boys are the dominant SLT users than girls. However, studies from the African region found that girls used SLT more than boys or no association. In general, higher level of parental education was inversely associated adolescent SLT use. Though, heterogeneity shown related to either of the parental education status and its association with adolescent SLT use. Majority studies linked to ethnicity and adolescent SLT use are from the US and agreed that white American adolescents are the main SLT users and African American smokes cigarettes. Regarding the place of residence all studies agreed that rural adolescents are more likely to be SLT users than urban adolescents. Studies related to adolescent access and availability of SLT products were limited. Social connections are main source of adolescent SLT. Compliance with TCA (Tobacco Control Act) concerning accessibility and exposure to tobacco advertisement was associated with increased adolescent SLT use. Based on previous studies, parental use is one of the strongest predictors of adolescent

SLT use. Heterogeneity present among the studies result related to higher risk associated with either mother or father SLT use status. All studies agreed to the strong role of friends SLT use status on adolescent SLT use. However, controversy remained related to friends smoking status and risk of adolescent SLT use. Despite controversy, friend's tobacco use status is the strongest predictor of adolescent SLT use. Articles linked to adolescent's knowledge about SLT related harm was very limited. Existing literature review result suggested that difference exist in knowledge and attitudes regarding SLT use and its related harm between users and non-users. However, question remained in their ability to predict adolescent SLT use status. Limited data is available related to Bangladeshi adolescent SLT use and its related factors. Only information related to Bangladeshi adolescent SLT use is the national prevalence. Further studies are needed to explore those factors contributing towards adolescent SLT use in Bangladesh.

2.2 A review of the oral cancer risk factors

2.2.1 Introduction

Oral cancer is a multifactorial disease. The major risk factors can be categorised as two main categories- behavioural (modifiable) and sociodemographic (non-modifiable). Most important behavioural risk factors of oral cancer are tobacco smoking, SLT use, alcohol drinking, HPV/sexual habit and diet. Important non-modifiable risk factors are socio-demographic status, age, gender (Petti, 2009). The aim of this section of the review is to examine the risk factors associated with oral cancer using the existing literature. Past studies that looked at the potential aetiological agents of oral cancer will be critically discussed. The review largely focused on behavioural risk factors. However, the effect of other putative risk factors such as oral hygiene, BMI (Body Mass Index) and family history of cancer were also explored.

2.2.2 Search strategy and article selection

An extensive search of the literature was conducted, including PubMed, ProQuest, ScienceDirect and Google scholar database. The search was carried out using various combinations of corresponding descriptors (MeSH) and free text terms such as

- oral cancer or mouth cancer or oral carcinoma or head and neck cancer or mouth neoplasm or oral neoplasm or Squamous cell carcinoma of oral cavity or carcinoma lip, or carcinoma tongue.
- Epidemiology or mortality or incidence or trends or prevalence.
- Case-control study or hospital-based case-control study or population-based case-control study
- risk factors or aetiology,
- smoking or cigar or filtered cigarettes or unfiltered cigarettes or bidi or hukkah or water pipe
- alcohol,
- Oral health or oral hygiene,
- Diet or dietary score, Mediterranean diet or Asian diet
- Body mass index or height or weight or body size or obesity or overweight, leanness
- family history or
- Viral hepatitis, HPV
- smokeless tobacco or chewing tobacco or betel quid or pan or naswar or ghutka or areca nut or betel nut

- Bangladesh or India or Pakistan or Sri Lanka or Nepal or South-Asia or South-east Asia or Europe or USA or Africa, Scandinavian

The search was restricted to study published in English until December 2018. The author of this thesis (ZU) had independently run the search. Initially tittles and abstract of the studies was screened based on inclusion and exclusion criteria defined specially for this study (see nest section). Final articles were including after the agreement of both supervisors. For the present review, original clinical studies including case-control study and cohort study were included where at least number of cases was 100. Due to the nature of this review (NR) few systematic reviews and meta-analysis was included in this review. However, all those reviews were based on case-control and cohort studies.

2.2.2.1 Study inclusion criteria

- Original studies published in peer-reviwed journals and specified atleast one or both genders.
- Stuides that had at-least 100 cases.
- The primary outcome of the study was clearly defined, oral cancer (ICD10: C00–C06).
- Exposure of interest was smoking tobacco, smokeless tobacco, alcohol, joint effect of alcohol and tobacco, oral health indicators, viral hepatistis, diet, and family history of cancer.
- Studies that provided odds ratios (OR) for case-control studies and relative risks (RR) for cohort studies, with their corresponding 95% confidence interval (CI).

- Studies that were published in English until December 2018.

2.2.2.2 Study exclusion criteria

- Cross-sectional study, survey, experimental studies, letters to the editor, unpublished data, and articles not published in English were excluded.
- Stuides with insufficient power (less than five expected case exposure).
- Other pathological and physiological studies on oral cancer risk factors.
- Studies with fewer than 100 cases.
- Articles related to oral pre-cancerious lesions such as oral leukplakia.

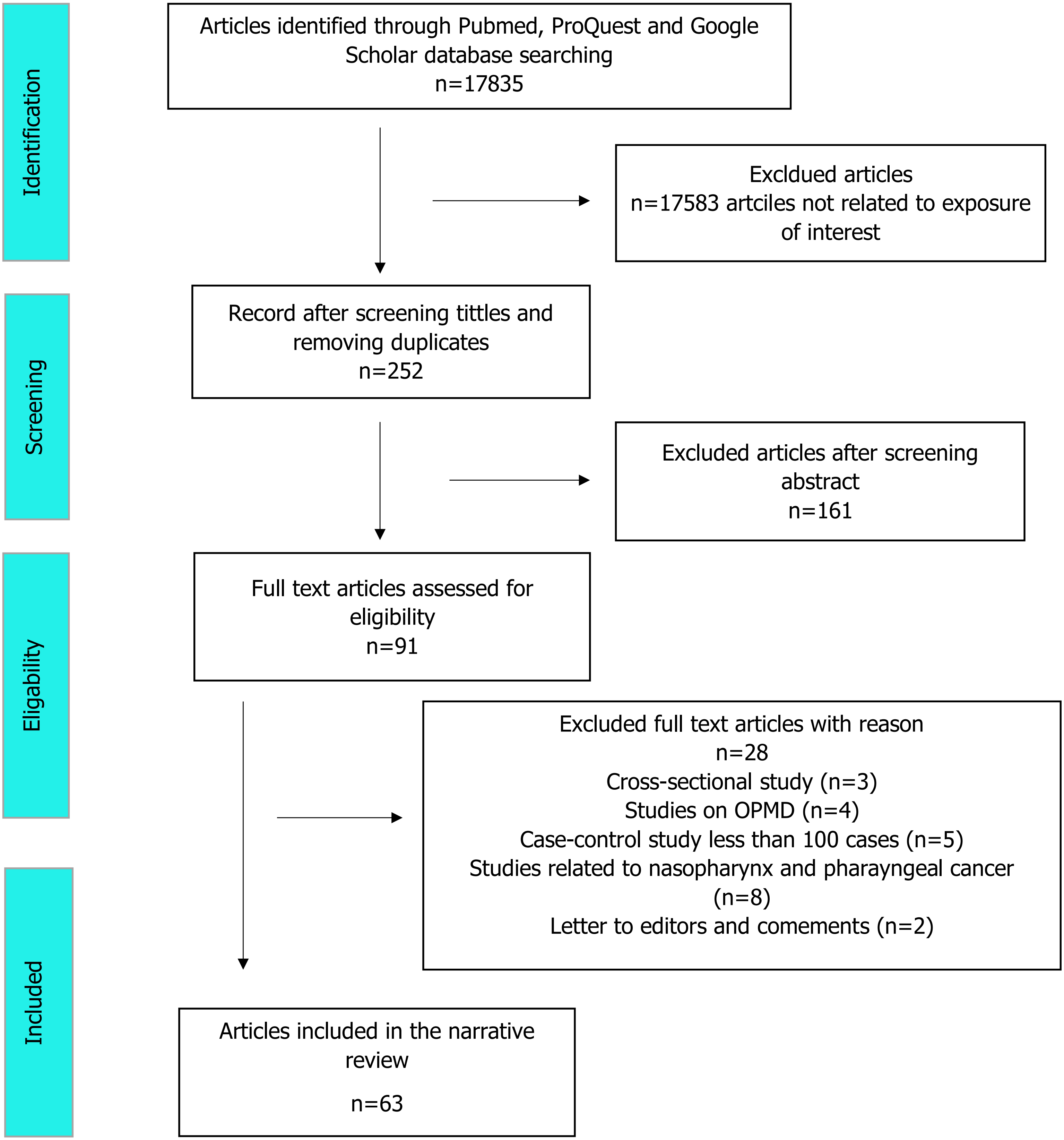


Figure 3b: Flow chart of articles selection process for the review

2.2.3 Oral cancer epidemiology

According to the National Cancer Institute (NCI, 2011), oral cancer is a cancer of the tissues of the oral cavity (the mouth) or the oropharynx (the part of the throat at the back of the mouth). Oral cancer may develop from a primary lesion initiated from any tissue in the mouth cavity, metastasis from a remote site or extension from another neighbour anatomical structure (e.g., nasal cavity). However, the literature lacks a standardised oral cancer definition. A review conducted by Tapia and Goldberg (2011) reported that 17 different terms are used for oral cancer in the literature. Another review of 102 articles revealed that the definition of oral cancer is not standardised because of the lack of uniformity in defining an oral cavity. As some articles suggested, the soft palate and base of the tongue is part of the pharynx, not the oral cavity, whereas the cutaneous lip, some sites of the pharynx and major salivary glands are often included in the oral cavity (Radoi and Luce, 2013).

Based on the WHO's (2016) International Classification of Diseases (ICD) codes from the 10th revision (ICD-10), the following sites are associated with oral cancer: ICD10, C00-Malignant neoplasm of inner lip, Excl.:skin of lip-C43.0, C44.0; ICD-10, C01-Malignant neoplasm of base of tongue; ICD-10, C02–Malignant neoplasm of other and unspecified parts of tongue; ICD-10, C03–Malignant neoplasm of gum; ICD-10, C04-Malignant neoplasm of floor of mouth; ICD-10, C05–Malignant neoplasm of palate; ICD-10, C06–Malignant neoplasm of other and unspecified parts of mouth; ICD-10, C09–

Malignant neoplasm of tonsil; ICD-10, C10–Malignant neoplasm of oropharynx; and ICD-10, C14–Malignant neoplasm of other and ill-defined sites in the lip, oral cavity.

2.2.3.1 Incidence

Cancer is the second-most common cause of global morbidity and mortality. Approximately six million people die every year because of cancer, and it is estimated that there will be over 15 million cases every year by 2020 (Khan, 2012). Among all cancers, oral cancer is the 11^{th}-most common cancer in the world. According to recent global cancer statistics by Bray *et al.,* (2018), 354,864 new oral cancer cases were diagnosed worldwide in 2018. Among all oral cancer cases, 45.9% of cases (159,750 of 354,864 new cases) were from South-Central Asia, 6.5% (22,706 of 354,864 new cases) were from Central and Eastern Europe and 7.5% (27,106 of 354,864 new cases) were from North America. Globally, the age-standardised rate (ARS) was higher among males (5.8) than females (2.3; Bray *et al.*, 2018).

A wide geographical variation in oral cancer incidence is evident, which is approximately 20-fold. Across various WHO regions, a considerable variation of oral cancer prevalence was reported (Table 9). The highest incidence rate was observed in the SEAR followed by the East Mediterranean region, and the lowest incidence rate was observed in the African region. Regarding 5 years of prevalence, the SEAR reported the highest number (331,321), followed by the European region (202,600). Across the WHO regions, males had a higher rate of incidence, mortality and prevalence (IARC, 2018).

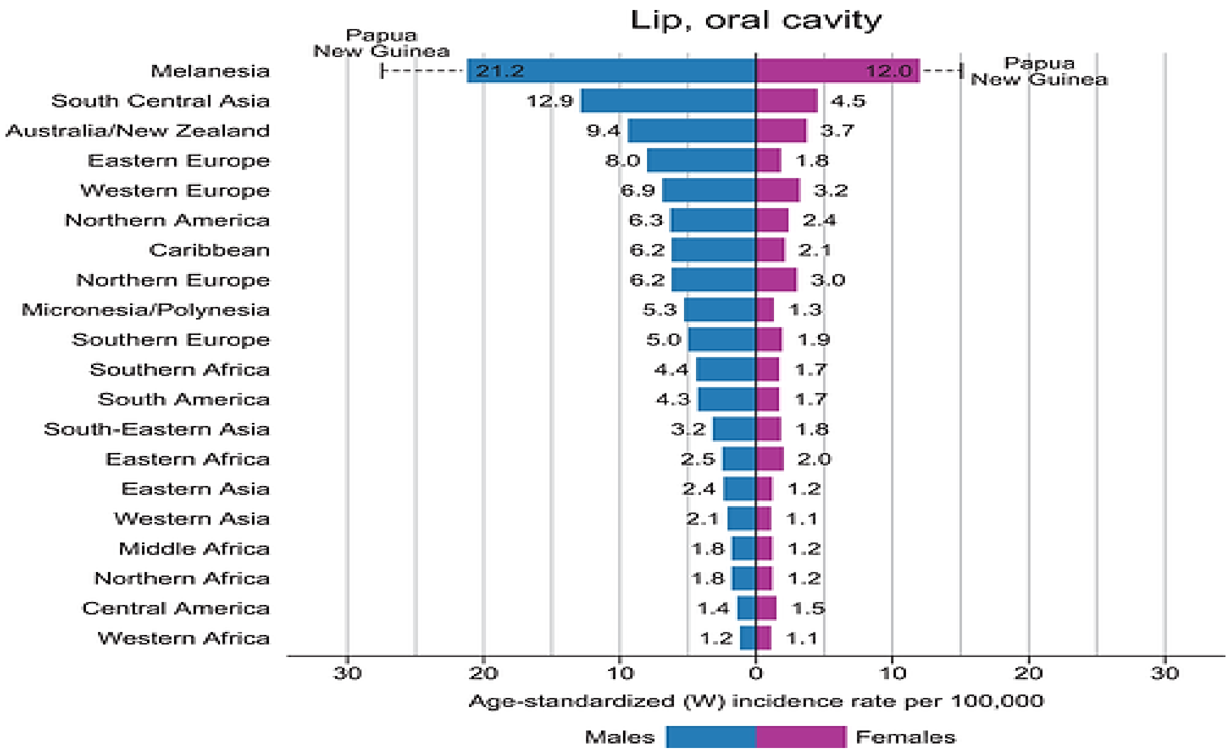


Figure 4: Oral cancer incidence and geographical variations. (Source: Bray *et al.*, 2018).

Most of the oral cancer incidences are from developing countries. Papua New Guinea had the highest age-standardised incidence rate of 20.4 (IARC, 2018). Oral cancer is the fourth-most common cancer in South-East Asia and ranks 1st among all the cancers in men, with an estimated 149,102 oral cancer cases diagnosed in 2018 (IARC, 2018). The age-standardised incidence rate in the SEAR is 7.6. India, Pakistan, Bangladesh and Sri Lanka are some of the high-risk countries from this region (Warnakulasuriya, 2009), with oral cancer being the most common cancer in India. India alone accounted for 34.5% (119,992 of 354,864 of new cases) of the total global oral cancer cases. In India, oral cancer accounts for 30%–40% of all malignant tumours compared to 2%–4% in Western countries (Byakodi *et al.*, 2012). In India, the estimated age-standardised incidence rate was 9.1 per 100,000 populations (IARC, 2018). Pakistan had the second highest oral cancer incidence rate in the world at 12.2 per 100,000 population and accounted for 5.8% (18,881 of 354,864 of new cases) of the global new oral cancer cases in 2018.

Oral cancer burden is much lower in developed countries compared to LMICs. In 2018, a total of 6,087 new oral cancer cases were diagnosed in the United Kingdom. The majority of these oral cancer cases were male (3,880) and were strongly associated with age (IARC, 2018). Based on the National Cancer Institute survey in the United States, 45,780 oral cancer cases were diagnosed, and 8,650 deaths were related to oral cancer in 2015, with the majority being male (32,670 vs. 13,110 females; Siegel, Miller and Jemal, 2015).

The significant regional variations of oral cancer incidences are likely to be associated with the relative distribution of specific risk factors (Shield *et al.*, 2017). For example, lip cancer is more common in Australia and some European countries and believed to be caused by ultra-violet rays and the transfer of heat from smoke (Czerninski *et al.*, 2010). In the Indian subcontinent, particularly in India, Pakistan, Bangladesh and Sri Lanka, and a substantial part of southern Asia, particularly in China and Thailand, higher incidences of oral cancer are associated with tobacco smoking and SLT use. Additionally, the oral cancer rate is higher in countries with a large population of Asian immigrants, such as the United Kingdom and other countries in Europe (Llewellyn *et al.,* 2001). In Western countries, oral cancer incidences are highly likely to be associated with alcohol consumption, tobacco smoking and human papilloma virus (HPV) infections (Bagnardi *et al.*, 2015). Historically, alcohol consumption and tobacco smoking are highest in northern America and European regions (WHO, 2014a), and the synergistic effect of alcohol and tobacco use may play a sizeable role in the oral cancer rate in these regions (Maasland *et al.*, 2014).

Table 9: Estimated incidence, mortality, and five years of prevalence of lip and oral cavity cancer.

Region		**Incidence**		**Mortality**		**5-years prevalence**	
		N (%)	**ASR (W)**	**N (%)**	**ASR (W)**	**N (%)**	**Prop**
World	Male	246,420 (2.6)	5.8	119,963 (2.2)	2.8	628,799 (3.0)	16.3
	Female	108,444(1.26)	2.3	57,615 (1.38)	1.2	284,715(1.25)	7.5
	Both Sex	354,864 (1.96)	4.0	177,384(1.87)	2.0	913,154(2.10)	12.0
WHO African region	Male	5,741 (1.7)	2.0	4,577 (2.0)	1.2	11,073 (2.1)	2.10
	Female	4,809 (1.0)	1.5	3,603 (1.19)	1.7	9,357 (1.02)	1.70
	Both Sex	10,550 (1.3)	1.7	8,207 (1.53)	1.4	20,430 (1.41)	1.90
WHO American Region	Male	31,406 (1.6)	5.0	9,012 (1.26)	1.4	97,240 (1.7)	19.4
	Female	15,604 (0.85)	2.0	4,060 (0.62)	0.46	47,200 (0.81)	9.20
	Both Sex	47,010 (1.24)	3.4	13,072 (0.95)	0.90	144,440 (1.3)	14.2
WHO East Mediterranean Region	Male	17,045 (5.2)	6.0	10,597 (4.7)	3.7	33,815 (5.7)	9.4
	Female	8,889 (2.5)	3.3	6,148 (3.1)	2.3	19,162 (2.5)	5.7
	Both Sex	25,934 (3.8)	4.7	16,745 (4.0)	3.0	52,977 (3.9)	7.6
WHO Europe Region	Male	44,753 (1.8)	6.3	18,573 (1.54)	2.6	137,837(2.16)	30.8
	Female	20,973 (0.98)	2.2	7,037 (0.75)	0.66	64,763 (0.99)	13.6
	Both Sex	65,726 (1.44)	4.1	25,610 (1.19)	1.5	202,600(1.57)	22.0
WHO South-East-Asian region	Male	110,710 (11.3)	11.3	61,129 (8.6)	6.3	242,781(14.4)	23.8
	Female	38,392 (3.8)	3.9	28,257 (4.5)	2.9	88,540 (4.0)	9.1
	Both Sex	149,102 (7.4)	7.6	89,377 (6.7)	4.6	331,321 (8.5)	16.7
WHO Western Pacific Region	Male	36,711 (1.07)	2.6	15,792 (1.09)	1.1	105,888(1.72)	10.7
	Female	19,764 (0.71)	1.3	8,556 (0.59)	0.50	55,662 (0.85)	5.9
	Both sex	56,475 (0.91)	1.9	24,348 (0.65)	0.79	161,540(1.27)	8.4

ASR (Age-standardised rate) (W) and proportions per 100,000. N – Number ASR (W) – Age-standardised rate WHO Prop -Proportion (Source: IARC, 2018)

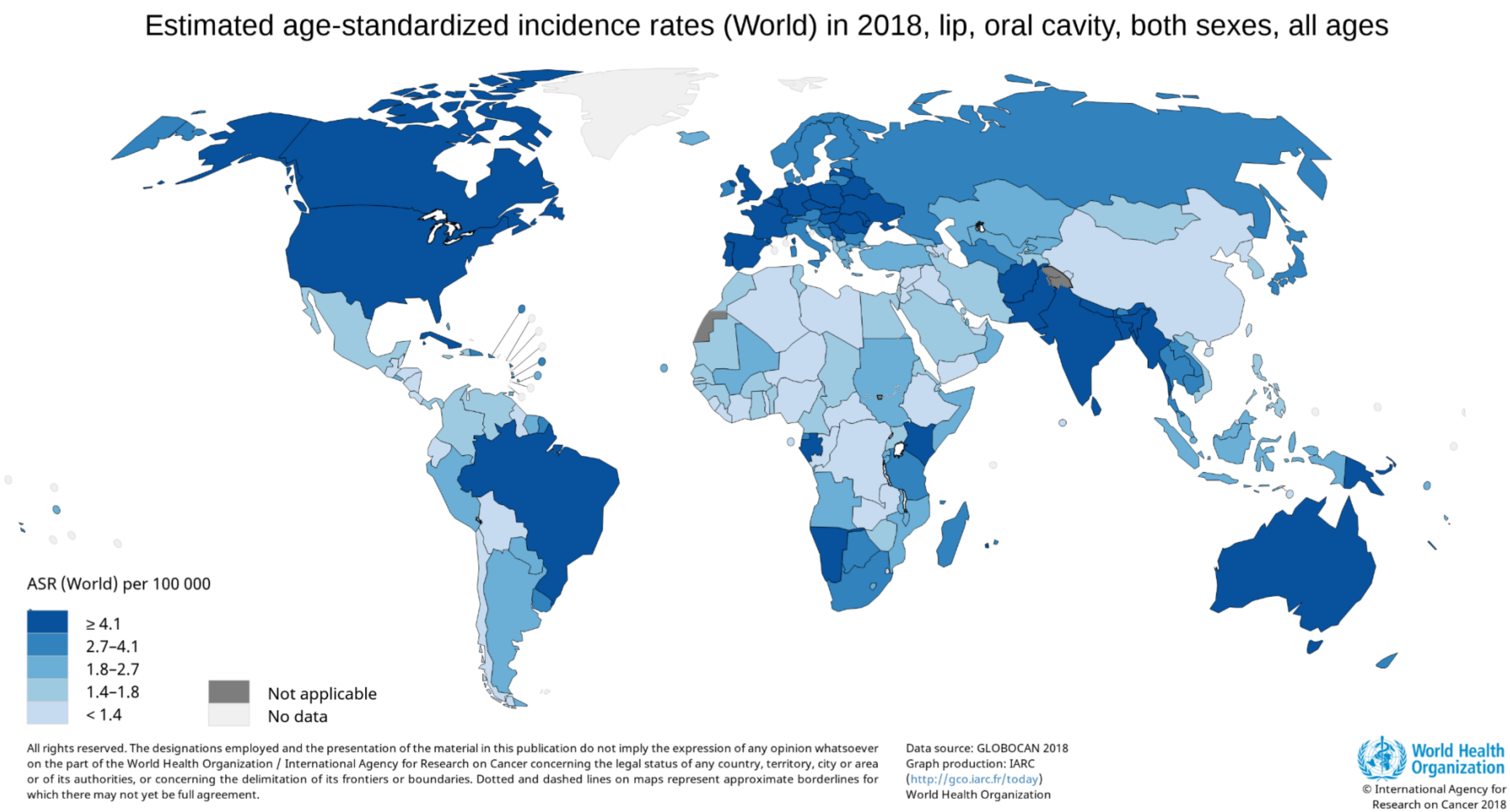


Figure 5: Age-standardised oral cancer incidence rate (Source: Bray *et al.,* 2018)

2.2.3.2 Mortality and survival

Every year worldwide an estimated 177,384 adults die because of oral cancer. Men have a higher mortality rate compared to women, the estimated mortality rate among men was 2.8 (per 100,000) compared to 1.2 (per 100,000) in women (IARC, 2018). Oral cancer mortality is particularly high in the WHO SEAR (4.6/100,000; see Table 9). Notable variations of oral cancer mortality are observed within countries. For instance, in the United States, mortality rates of oral cancer vary by more than five-fold. The combination of ethnicities, socio-economic statuses and variations in the prevalence and severity of risk factors in these communities, including the use of SLT in the southern states, can explain these regional differences (Gupta *et al.*, 2016). The most striking between-country difference is observed in the European Union, which has rates varying between 3- and 10-fold increases in oral cancer mortality rate between Central and Eastern Europe (Diz *et al.*, 2017).

The considerable mortality rate of oral cancer mainly depends on the stage of the disease at diagnosis; the earlier the cancer is diagnosed, the better the survival rate. The 5-year survival rate for stage I cancer is approximately 80% and approximately 20% for advanced stage (stage III/IV). Sadly, worldwide, approximately 50% of the oral cancer patients are diagnosed with advanced stages (Warnakulasuriya, 2009). Regarding the anatomical site, the best survival rate is seen in patients with cancer of the lip, with over 90% of patients surviving for 5 years. Women had a higher survival rate than men for cancer of both the tongue and the oral cavity (Warnakulasuriya, 2009). The survival rate is also significantly associated with behavioural risk factors and treatment options. Le campion *et al.,* (2017) stated that the survival rate after the initial oral cancer diagnosis was 59.3% in the first year, 40.7% in 2 years and 27.8% in 5 years and was significantly associated with alcohol intake, advanced cancer staging and procedure without surgery.

2.2.3.3 Trends

Worldwide, cancers of the lip and oral cavity are predicted to be increased by 29.9% by 2030 and the change is predicted to be higher among women (31.6%) compared to men (IARC, 2018). Among the WHO regions, the incidence rate increased in the South-Asian region, estimated ASR (Age-standardised rate) 7.6 in 2018 compared to 6.4 in 2012. The declining trend was observed in the WHO American region, estimated ASR was 3.4 in 2018 compared to 4.2 in 2012 (IARC, 2018). Among all genders, the incidence rate in the WHO SEAR increased substantially among men from 8.9 per 100,000 population in 2012 to 11.3 per 100,000 population in 2018.

Several other studies demonstrated oral cancer trends in different regions in the world. A recent study by Diz *et al.,* (2017) stated that the oral cancer incidence rate in Europe showed a declining trend. However, a high oral cancer incidence rate was observed in Denmark and for lip cancer in Spain. Moreover, a significant increase in oral cancer-related mortality was observed among women in most Eastern European countries. For example, Belarus observed a 61% increase in the oral cancer-related mortality rate when compared to the rate from 2000 to 2003. In Romania and Hungary, oral cancer-related mortality among men increased by over 30% between 1990 and 2004. Another recent study from the Oceania region reported the rate of oral cancer in this region is predicted to be increased by 49% by 2030 (Pollares *et al.*, 2017). The incidence and mortality rates are also projected to be doubled by 2030 in the African region, specifically in Egypt, Iran, Morocco, Sudan and Turkey (Kujan *et al.*, 2017).

2.2.3.4 Oral cancer scenario in Bangladesh

In Bangladesh, epidemiological data related to oral cancer is limited. Only estimated data is available from the WHO's IARC GLOBOCAN report. Bangladesh has the third-highest age-standardised oral cancer rate in the world (9.5 per 100,000 population). An estimated 13,401 new oral cancer cases were diagnosed in 2018 (see Figure 6). Oral cancer is the third-most common cancer among Bangladeshi men and fifth among women. Men have a higher incidence rate compared to women, with estimated age-standardised incidence rates being 12.4 per 100,000 and 6.5 per 100,000 population, respectively (IARC, 2018).

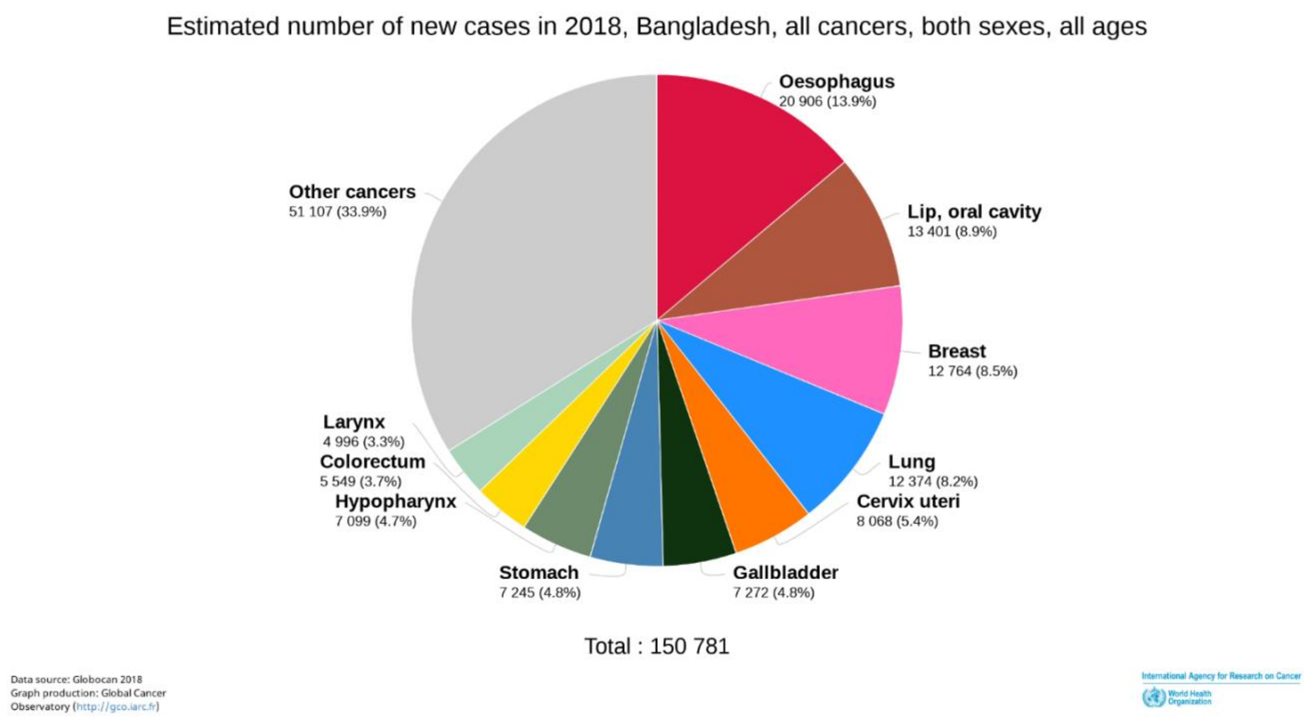


Figure 6: Estimated number of new oral cancer cases (both genders) (Source: IARC, 2018).

Overall, oral cancer is the third leading cause of cancer-related death in Bangladesh; in 2018, an estimated 8,570 adults died from oral cancer (see Figure 7) (IARC, 2018). Oral cancer is the third leading cause of cancer-related death for men and fifth leading cause of death for women.

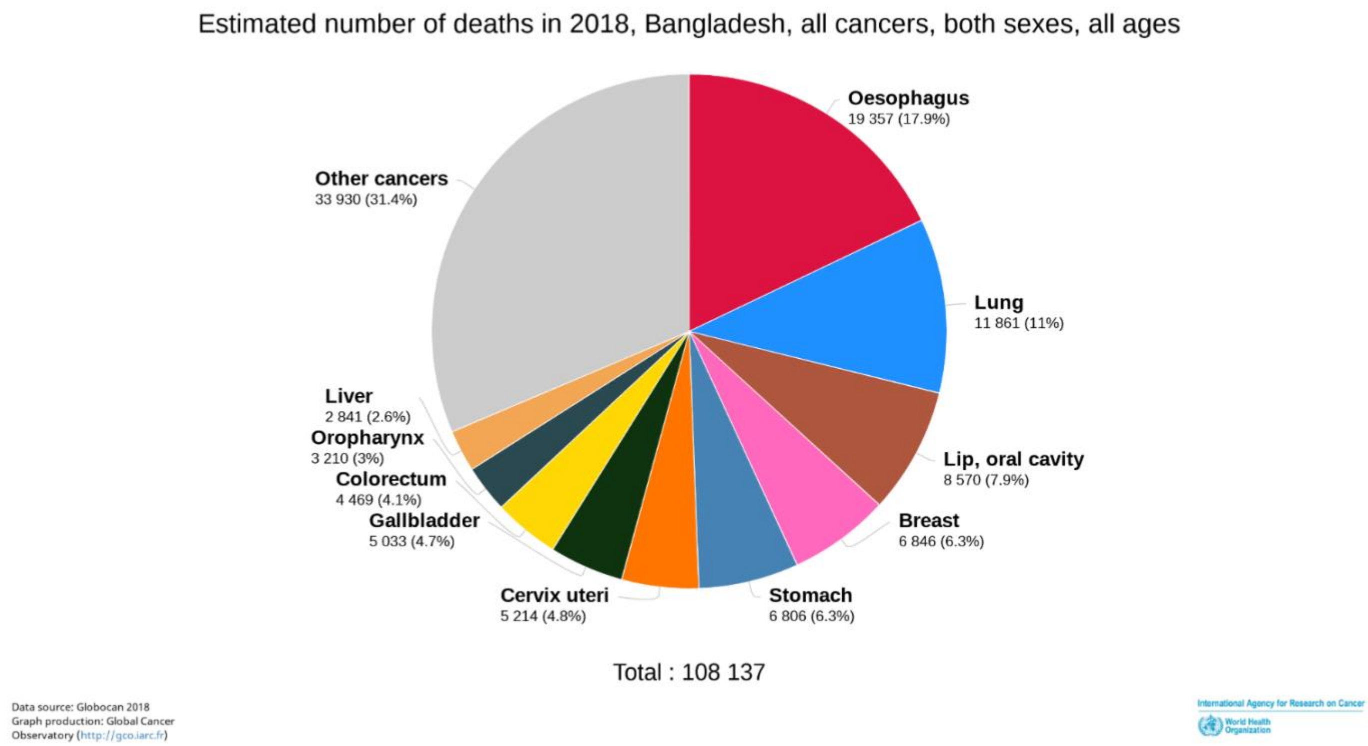


Figure 7: Estimated number of deaths related to oral cancer in Bangladesh. Source: IARC, 2018.

Based on the current trends and considering the demographic and risk factors, an estimated additional 6,255 new oral cancer cases and 4,263 deaths related to oral cancer are expected by 2030; an increase of 46.7% from 2018 (IARC, 2018). A larger portion of these cases will be among men (3,908) compared to women (2,347).

2.2.4 Risk factors for oral cancer

Many types of exposures have been investigated as possible risk factors for oral cancer development. Lifestyle behavioural risk factors, such as tobacco smoking, SLT chewing and alcohol drinking, are considered as major risk factors (Warnakulasuriya, 2009b). According to Johnson (2001), smoking, tobacco chewing, heavy alcohol drinking, and poor diet together accounted for 90% of oral cancer cases. Several other emerging risk factors, such as HPV, oral health indicators, body mass index and family history of oral cancer, also had a possible role in oral cancer development (Warnakulasuriya, 2009b). Below is review of the relevant studies related to oral cancer risk factors.

2.2.4.1 Tobacco

The role of tobacco in oral cancer development has been studied extensively. Early studies established tobacco use as an independent risk factor of oral cancer (Andre *et al.*, 1995; De Stefani *et al.*, 1998; Moreno-López *et al.*, 2000; Zavras *et al.*, 2001; Llewellyn *et al.*, 2004; Warnakulasuriya, Sutherland and Scully, 2005; Ernani and Saba, 2015). Tobacco, whether it is smoked, chewed or inhaled, is considered as a major carcinogen. Hence, the IARC (2012) regarded tobacco as Class-I carcinogens for oral and pharyngeal cancer. In the following sections, different forms of tobacco, namely SLT and smoked tobacco, and their association with oral cancer development are discussed.

Smokeless tobacco

Based on the available evidence, the IARC (2012) declared traditional SLT, such as BQ (Betel Quid), snuff and chewing tobacco, as carcinogenic to humans and concluded sufficient evidence exists to confirm SLT causes oral pre-cancerous lesions and cancer of the oral cavity. The total burden of SLT-related cancer is likely to be substantial with over 300 million SLT users worldwide (NCI and CDC, 2014). Since SLT products are placed in the mouth or sniffed, there has always been a concern that their use will cause cancer in the oral cavity, pharynx or larynx (Colilla, 2010). The possible relationship between SLT use and oral cancer has been studied since the early 19th century. In 1915, Abbe found that 33 out of 100 mouth cancer patients were heavy smokers, 13 of these smokers were chewing tobacco users and one was oral snuff user (Abbe, 1915). In 1933, Orr reported that using, for example, shell lime and jaffna tobacco (very cheap and irritating tobacco), prolonged the retention of quid in the mouth and this coupled with a diet low in vitamins increased the risk of having oral cancer in some parts of India (cited in Gupta and Johnson, 2014). Detailed evidence of SLT use and risk of oral cancer is discussed later in the literature review.

Smoked tobacco

Tobacco smoking is one of the major risk factors for oral cancer. Based on epidemiological studies, smoking is the leading cause of oral cancer for both men and women. Also, any method of smoking, whether it is cigarettes, pipes or bidi, is associated with increased oral cancer risk (Blot *et al.*, 1988; Petti *et al.*, 2013; Mahapatra *et al.*, 2015). This association is stronger for increased frequency and duration of use for of all types of smoking; however, a sharp reduction in oral cancer risk is seen following smoking cessation (Marron *et al.*, 2010).

A meta-analysis of observational studies from South-Asia by Petti *et al.,* (2013a) reported that the pooled odds ratio for oral cancer from smoking was 3.6 (95% CI [1.9, 7.0]) and synergistic effects were seen for smoking, chewing and drinking. As suggested by Petti *et al.,* (2013a), among smoking–drinking–chewing subjects in SEAR, individual effects accounted for 6.7% for smoking, 3.1% for alcohol drinking and 17.7% for chewing of the oral cancer risk, while the interaction effects among these factors accounted for the remaining 72.6%.

The risk of oral cancer appears higher among heavy smokers. A large case-control study from Sau-Paulo Brazil reported that the odds of oral cancer for moderate smoking and heavy smoking was 2.65 (95% CI [2.07, 3.38]) and 7.43 (95% CI [5.94, 9.30]), respectively. Additionally, ever smoking was associated with a five-fold increased risk of oral cancer (Antunes *et al.,* 2013). However, a case-control study from Trivandrum, India did not find any effect of smoking on oral cancer risks in males after adjusting for SLT use and alcohol drinking. Though, they found significant increased risk of oral cancer among bidi smoking alone, OR = 1.9, 95% CI [1.1, 3.2], compared to never smokers (Muwonge *et al.*, 2008).

Some studies have demonstrated a dose-dependent relationship between tobacco smoking and oral cancer risk, with the risk of oral cancer increasing with the frequency of smoking per day and total duration of smoking (Subapriya *et al.,* 2007; Lee *et al.,* 2019). A case-control study from India reported that smoking less than five gm/day of tobacco was associated with a nearly two-fold increased risk of oral cancer and the risk went up to over six-fold for smoking five gm of tobacco or more per day. Additionally, smoking less than 10 years increased the risk by two-fold and more than 40 years of smoking increased it by nearly four-fold (Subapriya *et al.*, 2007). Similar findings were reported in a large multicentre hospital-based case-control study from East Asia (921 cases; 806 controls): an increased risk of oral cancer was found among ever smokers, OR = 1.58, 95% CI [1.18, 2.13], and smoking over 20 cigarettes a day and smoking for 20 years or more increased the risk substantially compared to non-smokers (Lee *et al.,* 2019).

Several case-control studies analysed the relationship between age of smoking onset and oral cancer risk. Early studies conducted in Italy by Franceschi *et al.*, (1992) and India by Sankaranarayanan *et al.*, (1990) found starting smoking at an early age was associated with an increased risk of oral cancer. Another hospital-based case-control study including 187 oral cancer cases and 240 controls from India found that respondents who started smoking at 24 years of age or less were two times more likely to have oral cancer compared to non-smokers and the association remained significant after adjustment for other covariates (Gupta *et al.*, 2017). However, contrary findings were reported by Balaram *et al.,* (2002), who did not find a significant relationship between age of onset of smoking and oral cancer.

Other smoking factors also appear to affect the risk of oral cancer, such as not using filters. An early case-control study from the United States found that lifelong filter smokers observed only one-half the oral cancer risk of non-filter smokers (Blot *et al.*, 1988). However, a case-control study including 319 men and 428 controls in China analysed the relationship between oral cancer risk and smoking filtered and non-filtered cigarettes (Fu *et al.*, 2013). The study results concluded no apparent protective effect of filtered cigarettes. As compared with non-smokers, the adjusted odds ratios for oral cancer were 1.30 (95% CI [1.15, 1.48]) for filtered cigarette smokers, 2.06 (95% CI [1.17, 3.62]) for non-filtered cigarette smokers and 1.73 (95% CI [1.33, 2.25]) for mixed smokers, but these differences were not statistically significant.

Previous studies have also examined the risk of oral cancer from different types of smoking tobacco, such as cigarettes, cigars, pipes and hand-rolled cigarettes as well as traditional tobacco in Asia, such as bidis and cheroot (Radio and Luce, 2013). Regarding the type of smoked tobacco and the risk of developing oral cancer, the results varied substantially. Previous case-control studies from India found that smoking pipes and cigars pose a higher risk of developing oral cancer (OR = 4.28 to 10.17) compared to manufactured cigarettes (OR = 1.08 to 1.79; Balaram *et al.*, 2002; Znaor *et al.*, 2003).

Several studies from South-Asia found that traditionally manufactured smoked tobacco, also known as bidi, increased oral cancer risk substantially. Bidi is an indigenous form of smoking widely used by people with low SES in India, Bangladesh, Nepal, Pakistan and other South-Asian countries (Vyas *et al.*, 2018). Regarding the risk of oral cancer development from bidi smoking, a meta-analysis of South-East-Asian studies revealed that bidi smoking increases oral cancer risk by three-fold compared to never smokers, and the relationship was stronger with longer duration of smoking (Rahman *et al.*, 2003). Similar findings were reported by Madani *et al.,* (2012), who found a significant association between bidi smoking and oral cancer risk, OR = 4.1, 95% CI [2.4–6.9], and the association showed dose-response dependence. A large cohort study among 66,277 men aged 30–84 years from Kerala, India found that bidi smoking is an independent risk factor for oral cancer risk, RR= 2.6, 95% CI [1.4 – 4.9], and the risk increased with higher daily bidi consumption, longer duration and starting bidi at a younger age (Jayalekshmi *et al.*, 2011).

According to the GATS (2009), there are estimated 24.1 million current smokers in Bangladesh, and among these, 13.5 million smoked manufactured cigarettes, 10.6 million smoked bidis and 1 million smoked hand-rolled cigarettes, pipes and water pipes (hukkah). Research has yet to be carried out to explore the possible association between smoking and oral cancer risk among Bangladeshi adults. Table 10 represents the key studies outlined above and their significant findings related to oral cancer risk from smoking tobacco.

Table 10: Previous case-control studies related to smoking and risk of having oral cancer

Autor	**Region**	**(case: control)**	**Gender**	**Matching factors**	**Variables**	**OR (95%CI)**
Fu *et al*., (2013)	China	(390:428)	Male	Age	Filter cigarette smoker	1.30 (1.15-1.48)
					Non-filter cig smokers	2.06 (1.17-3.62)
					Mixed smokers	1.73 (1.33-2.25)
					Pack-year < 20	1.16 (0.89-1.50)
					Pack-year 20-39	1.32 (1.12-1.57)
					Pack-year ≥40	2.93 (2.13-4.03)
Mahapatra *et al*., (2015)	India	(134:268)	Male, female	Age, gender	Bidi smoking	2.30 (1.10-4.80)
Balaram at al., (2002)	India	(591:582)	Male, female	Age, gender, study centre	Former smoker	1.38 (0.78-2.47)
					Current cig smoker	1.08 (0.56-2.09)
					Current Cigars smoker	10.17 (1.12-92.18)
					Bidi ≥20 per day	2.50 (1.41-4.42)
Muwonge *et al*., (2008)	India	(282:1,410)	Male, female	Age, gender	Current smoker	1.20 (0.80-2.8)
					Bidi smoking	1.90 (1.10-3.70)
					>20 bidi per day	1.60 (0.90-2.90)
Znaor *et al*., (2003)	India	(1,563:3,633)	Male, female	Age, gender	Current smoking	1.91 (1.61-2.26)
					Smoking >40 years	1.60 (1.25-2.06)
					Daily smoking ≥20	1.99 (1.47-2.68)
					Cigarettes only	0.99 (0.79-1.23)
					Bidi only	2.15 (1.75-2.63)
					Cig+bidi	1.49 (1.18-1.88)
					Cigar only	4.72 (2.41-9.25)
Gupta *et al*., (2017)	India	(187:240)	Male, female	Age, gender	Ever smoking	1.96 ((1.05-3.66)
					Age of onset (1-24)	2.55 (1.22-5.32)
					Consumption of bidi/cig per day >10	2.74 (1.28-5.89)
					Cumulative years of smoking (>200 years)	3.63 (1.67-7.89)

Autor	Region	(case: control)	Gender	Matching factors	Variables	OR (95%CI)
Sankaranarayanan *et al.*, (1990)	India	(414:895)	Male, female	Age, gender,	Ever bidi smoking	4.21 (2.09-8.45)
					Ever BQ with tobacco	14.28 (8.21-28.43)
					Ever bidi + ever BQ	21.46 (11.94-38.54)
Winn *et al.,* (2015)	North America, Europe, Latin America and Asia	(25,500:37,100)	Male, female	Age, Gender	Ever smoking	2.13 (1.53–2.98)
					Cigarette smoking	3.46 (3.24–3.70)
					Cigars	2.54 (1.93–3.34)
					Pipes	2.08 (1.55–2.81)
Lee *et al.,* (2019)	China, Taiwan	(921:806)	Male, female	Age, gender ethnicity, residence area	Ever smoking	1.58 (1.18-2.13)
					≥20 cigarettes per ay	1.78 (1.29-2.47)
					≥ 40 years smoking	1.76 (1.08-2.85)
Antunes *et al.,* (2013)	Sao Paulo, Brazil	1,144:1,661	Male, female	Age, gender	Ever smoking	5.04 (4.07-6.23)
					Level-1 smoker	2.65 (2.07-3.38)
					Level-2 smoker	7.43 (5.94-9.30)
Subapriya *et al.,* (2007)	Southern India	388:388	Male, female	Age, gender	Smoking	3.63 (none reported)
					bidi	4.63(none reported)
					Cigarette	2.33(none reported)
					≥5.0 gm tobacco/day	6.11(none reported)
					>40 years smoking	3.89(none reported)

2.2.4.2 Alcohol

Each year, approximately 3.3 million deaths and 4.5% of the global burden of diseases and injuries are attributable to alcohol drinking (WHO, 2014a). Based on the available epidemiological evidence, IARC (2012) concluded that alcoholic beverages are carcinogenic to the tissues in the mouth and throat and several other sites, most notably the oesophagus, larynx and liver. A higher risk of cancer is associated with a higher level of consumption, as even one drink per day can increase the risk significantly (Nelson *et al.*, 2013; Rehm and Shield, 2013).

The independent effect of alcohol on oral cancer is inconsistent and varies globally. An extensive pooled analysis of case-control studies reported that among never smokers the association of alcohol drinking and oral cancer was weak and statistically insignificant, OR = 1.18, 95% CI [0.93, 1.50] (Hashibe, *et al.*, 2007). Nevertheless, an increasing number of alcoholic drinks per day was associated with a higher risk of oral cancer but did not show any clear dose-response relationship. The pooled analysis also showed that only 7% of the cases of HNC were associated with alcohol drinking among never smokers (Hashibe *et al.*, 2007). In contrast, another systematic review of 52 studies reported a dose-response relationship between alcohol and oral cancer risk (Bagnardi *et al.*, 2015). The meta-analysis showed every category of alcohol consumption was associated with oral cancer in a dose-risk manner: light drinking, RR = 1.13, 95% CI [1.00, 1.26]; moderate drinking, RR = 1.83, 95% CI [1.62, 2.07]; and heavy drinking, RR = 5.13, 95% CI [4.31, 6.10] (Bagnardi *et al.*, 2015).

Some study results suggested an overestimation of oral cancer risk associated with alcohol use has occurred because researchers have not considered the alcohol and tobacco interaction in oral cancer development. A large hospital-based case-control study from Sao Paulo (Brazil) based on 1,144 oral cancer cases and 1,661 controls found over a three-fold increase risk of oral cancer from alcohol drinking, OR= 3.60, 95% CI [2.86, 4.53] and for smoking, OR = 3.50, 95% CI [2.76, 4.44]. However, when the interaction between alcohol and tobacco was considered, drinking was not independently associated with oral cancer, OR = 0.78, 95% CI [0.48, 1.27] and the independent effect of smoking was lowered considerably, OR = 1.41, 95% CI [1.02, 1.96] (Antunes *et al.*, 2013). A similar conclusion was made by a recent meta-analysis of seven studies between 2010 and 2012, which showed that alcohol drinking was inversely associated with oral cancer in non-smokers and non-BQ chewers, OR = 0.70, 95% CI [0.51, 0.96] (Petti *et al.*, 2013b).

An increasing number of alcoholic drinks per day and its association with a higher risk of oral cancer was reported in a recent prospective cohort study from the Netherlands (Maasland *et al.,* 2014). Drinking 30 grams or more per day of alcohol was associated with a significantly increased risk of oral cavity cancer, RR = 6.39, 95% CI [3.13, 13.03]. Although beer and wine drinking did not show any increased risk, drinking two or more glasses per day of liquor was associated with a two-fold increased risk of oral cancer, RR = 2.26, 95% CI [1.02, 4.99] (Maasland *et al.,* 2014).

Although a few studies have reported the effect of age at onset of drinking alcohol on oral cancer risk, they failed to establish a relationship between the two factors. For instance, a recent hospital-based case-control study of 187 oral cancer cases and 240 controls from India did not find any statistically significant associations between alcohol (type, age at onset, total duration and daily frequency) and oral cavity cancer (Gupta *et al.*, 2017). Similarly, a study from Southern India did not find any association between age at initiation and risk of oral cancer development (Balaram *et al.*, 2002)

Regarding the type of alcohol, study results are mixed. Several studies stated that oral cancer risk seemed to be independent of the type of alcohol consumed, whereas other studies found certain types of alcoholic beverages increased oral cancer risk and other did not find any association. A case-control study from Trivandrum, India found that any type of alcohol increased the risk of oral cancer (Muwonge *et al.*, 2008). Similarly, the case-control study by De Stefani *et al.*, (2006) found that beer and hard liquor showed a higher risk of oral cancer compared to wine. In contrast, another case-control study from China reported an insignificant association between types of alcohol and oral cancer risk (Wang *et al.*, 2015).

Alcohol consumption in Bangladesh is estimated to be much lower than the global average. Based on the Non-Communicable Disease Risk Factor Survey Bangladesh 2010, only 5.6% of Bangladeshi adults ever drank alcohol and only 2.0% of adults drank alcohol within the last year (Islam *et al.*, 2017). However, alcohol consumption in Bangladesh is on the rise; an increase in local production, an increasing number of permits for alcohol sales and a massive amount of captures of illegal alcohol indicate the actual amount of alcohol use might be much higher than officially reported (Gourab and Chowdhury, 2015). Again, research has yet to be conducted in Bangladesh to establish an association between alcohol drinking and the risk of oral cancer.

2.2.4.3 Joint effect of tobacco and alcohol

Studies have shown that the oral cancer risk in individuals exposed to smoking and drinking in combination is often higher than the sum of the individual risk of each. Such additional risk occurs because of the dual exposure, which is termed as the interaction or joint effect (Petti *et al.,* 2013). A large case-control study conducted by Antunes *et al.,* (2013) showed the individual adjusted odds ratio for oral cancer risk was 1.41 (95% CI [1.02, 1.96]) for smoking and 0.78 (95% CI [0.48, 1.27]) for drinking. However, the synergistic effect of smoking and drinking showed the highest risk, OR = 8.16, 95% CI [2.09, 31.78]. This view is also supported by a multicentre case-control study (17 centres from America and study from 14 centres in Europe) that found 40% of oral cancer cases were attributed to the joint effect of smoking and consuming alcohol (Hashibe *et al.*, 2009).

The joint effect of smoking and alcohol consumption in the South-Asia and Asia-Pacific region is worsening with the added burden of SLT use. Tobacco in both forms, smoking and smokeless, is widespread in South-Asia (Gupta and Ray, 2004; Giovino *et al.*, 2012). The likely joint effect of smoking–drinking–SLT use in the SEAR was first studied by Notani in (1988), who found that an individual who is exposed to multiple risk factors was 50 times more likely to have oral cancer compared to one who is not. A meta-analysis of observational studies in South-Asia revealed that the magnitude of the smoking–drinking–chewing interaction effects on oral cancer is significantly higher than individual effects (see Table 11; Petti, Masood and Scully, 2013). While estimating the interaction effects, the individual effects accounted for 6.7% (smoking), 3.1% (drinking) and 17.7% (chewing) of the risk, whereas the interaction effect accounted for the remaining 72.6%. This result suggests that each year among the 44,200 new oral cancer cases in South-Asia, 40,400 cases were exclusively associated with the interaction effects of smoking–drinking–chewing (Petti *et al.,* 2013).

Table 11: Pooled ORs and 95% CI for oral cancer adjusted for publication bias in the various exposure categories

Smoking	**Drinking**	**Chewing**	**Pooled (OR)**	**95% CI**
Yes	No	No	3.63	1.94-7.04
No	Yes	No	2.20	1.62-2.98
No	No	Yes	7.90	6.71-9.30
Yes	Yes	No	6.29	5.41-7.32
Yes	No	Yes	16.02	13.67-18.75
No	Yes	Yes	10.44	8.02-13.60
Yes	Yes	Yes	40.09	35.06-45.83

(Source: Petti, Masood and Scully, 2013)

In South-Asia, men are predominantly exposed to tobacco smoking and alcohol and women are exposed to SLT. Therefore, the joint effect of smoking–alcohol–chewing on oral cancer risk is likely to be more relevant to male users. This issue was identified in a case-control study from India (Gupta, Kumar and Johnson, 2017) that found the synergistic effects of smoking–drinking–chewing showed the highest risk, OR = 12.5, 95% CI [4.61, 31.49], followed by smoking–chewing, OR = 8.64, 95% CI [2.63, 28.37] and chewing tobacco alone, OR = 7.65, 95% CI [3.12, 18.75]. The study findings additionally showed no population attributable risk associated with alcohol use. However, the joint effects of chewing, smoking and alcohol drinking showed the highest population attributable risk at 86.82% (95% CI [72.20, 101.43]) among men. However, among women, the population attributable risk was only associated with SLT use, Attributable Fraction= 90.63%, 95% CI [80.01, 101.25] (Gupta *et al.,* 2017).

2.2.4.4 Oral health indicators

Poor oral hygiene and oral health status were identified as possible independent risk factors for oral cancer. A pooled analysis of 13 studies consisting of 8,925 incident cases and 12,527 controls exhibited an inverse association between oral cavity cancer and missing less than five teeth, OR = 0.69, 95% CI [0.64, 0.76], annual dental visit, OR = 0.82, 95% CI [0.76, 0.89], daily toothbrushing, OR = 0.81, 95% CI [0.75, 0.88], and no-gum disease, OR = 0.83, 95% CI [0.77, 0.89] (Hashim *et al.*, 2016).

A case-control study from China included 317 cases and 297 controls reported similar findings (Chang *et al.*, 2013). Poor dental care and poor oral health status (frequent gum bleeding and missing more than 20 teeth) were significantly associated with oral cancer risk after adjusting for cigarette smoking, alcohol drinking and BQ chewing. Overall, individuals with poor oral hygiene scores had a six-fold increased risk of oral cancer compared to those with good oral hygiene (Kawakita *et al.*, 2017).

Despite positive indications about the association between oral health indicators and oral cancer risk, several studies suggested that the association is likely to be confounded by other independent factors (e.g., tobacco and alcohol; Mathur *et al.*, 2019). A recent multicentre case-control study from India showed that poor oral hygiene significantly increased oral cancer risk, OR = 14.74, 95% CI [6.49, 33.46] (Gupta *et al.*, 2017). However, the study failed to show the risk among non-SLT users, thus evidenced the residual effects of tobacco use. In contrast, a recent study among Chinese women (non-smokers and non-alcohol drinkers) found that wearing dentures, oral ulceration and a loss of more than five teeth were significantly associated with oral cancer (Chen *et al.,* 2017).

Chronic dental trauma or irritation resulting from sharp teeth, dentures and faulty restoration are frequently reported as possible oral cancer risk factors. For instance, a case-control study from India reported a 13-fold increased risk of oral cancer from dental trauma (Dholam and Chouksey, 2016). However, the researchers failed to consider the confounding effect of independent risk factors, such as tobacco and alcohol. To eliminate the potential confounding effect on the relationship between dental trauma and oral cancer development, Perry *et al.*, (2015) examined the risk of oral cancer development among smokers and non-smokers. The researchers found that oral cancer occurred on the lateral border of the tongue from chronic dental trauma among 66% of non-smokers compared to smokers/ex-smokers (33%; $p < .001$). Table 12 lists several studies related to oral health indicators and risk of oral cancer development and their significant findings.

Table 12: Previous case-control studies related to oral cancer risk from poor oral health

Autor	Region	Design (case: control)	Gender	Matching	Variables	OR (95%CI)
Marques, *et al.*, (2008)	Brazil	Case-control (309:468)	Male and female	Age, gender	Gum Bleeding	3.10 [1.21–7.90]
					Never visited dentist	2.50 [1.34–4.80]
					Daily mouthwash use	3.20 [1.62–6.30]
Dholam and Chouksey, (2016)	India	Hospital-based case-control (85:85)	Male and female	Age, gender	Bad oral hygiene	17.40 [5.85–51.68]
					Dental Trauma	13.42 [3.89–46.29]
Chen *et al.*, (2017)	China	Hospital-based case-control (250:996)	Female	Age	Tooth brushing twice or more daily	2.23 [1.14–4.34]
					Wearing denture	1.68 [1.08–2.62]
					The loss of more than five teeth	2.84 [1.10–7.34]
					oral ulceration	5.77 [2.33–14.31]
Kawakita *et al.*, (2017)	China	Multicentre Hospital-based case-control study	Male and Female	Age, ethnicity, residence	No dental visit	3.70 [2.51-5.45]
					Frq of teeth cleaning one time/day	1.49 [1.11–1.99]
					≥5 missing teeth	1.49 [1.08-2.04]
Chang *et al.*, (2013)	Taiwan	Hospital-based case-control (317:296)	Male and Female	Age, gender	No dental visit	2.86 [1.47-5.47]
					Brushing < 2 times daily	1.51 [1.02 -2.23]
					Frequent gum bleeding	3.15 [1.36-7.28]
					Loss of > 20 teeth	2.31 [1.05-5.07]
Gupta *et al.*, (2017)	India	Hospital-based case-control study (187:240)	Male and female	Age, gender	Gum Bleeding	3.94 [2.49–6.25]
					Freq. of teeth cleaning ≤1	2.16 [1.18–3.93]
					Using stick or finger to clean teeth	1.29 [0.79–2.09]
					Cleaning substance	3.41[1.90–6.12]
					Dental check-up (only when had pain)	3.84 [2.38–6.20]
					Missing teeth>5	2.04 [1.08–3.86]
					Oral Hygiene score	6.98 [3.72–13.05]
Hashim *et al.*, 2016	United States, Europe, Latin America, Japan	Hospital-based case-control study (8,925:12,527)	Male and Female	Age, gender	Missing teeth <5	0.69 [0.64–0.76]
					Annual dental visit	0.82 [0.76–0.89]
					Daily toothbrush	0.81 [0.75–0.88]
					No-Gum disease	0.83 [0.77–0.89]

2.2.4.5 Body mass index

Tobacco and alcohol are two major risk factors of oral cancer. However, a large proportion of oral cancer patients exist who are non-smokers and non-drinkers, indicating that other factors may affect the risk of oral cancer (Gaudet *et al.,* 2010). Previous studies have found that individuals with a lower BMI (body mass index) have a higher risk of developing oral cancer (Rodriguez *et al.*, 2004; Kreimer *et al.*, 2006; see Table 13). However, the independent effect of BMI on oral cancer is challenging to assess, as BMI is strongly affected by smoking and drinking alcohol.

A large hospital-based case-control study of 375 incident cases and 375 age- and gender-matched controls from Spain found that a low BMI at diagnosis and 2 years prior to diagnosis were significantly associated with increased oral cancer risk, OR = 3.64, 95% CI [2.72,5.82] and OR = 3.31, 95% CI [2.04, 5.39], respectively (Nieto *et al.,* 2003). However, when examined in relation to smoking status, the association lost its significance and was only significant for past smokers at the time of diagnosis. For current smokers, leanness was associated with an increased risk of oral cancer at any point in time. This indicates that due to exposure to an elevated level of carcinogens, smokers may suffer from weight loss as a result of nutritional deficiency. Therefore, low BMI could be the result of smoking (Plurphanswat and Rodu, 2014). Nevertheless, the results of this study must be considered with care, as the BMIs were self-reported and may question their validity because of potential recall bias.

Contrary to this finding, a large multicentre population-based case-control study, ICARE (International Cancer Alliance for Research and Education) study in France did not find any residual confounding effects from smoking and drinking (Radoi *et al.*, 2013a). The study findings showed a reduced risk of oral cavity cancer among over-weight and obese people and even people who gained weight during their adulthood. After adjusting for smoking and drinking, those who were under-weight were six times more likely to have oral cancer compared to those who were obese, OR = 6.25, 95% CI [3.74, 10.45] (Radoi *et al.*, 2013a). The adjusted OR for smoking and alcohol showed no residual confounding.

Similar to the case-control study, a large population-based prospective cohort study among 5.24 million UK adults investigated the association between BMI and site-specific cancer (Bhaskaran *et al.*, 2014). The researchers found a low BMI is associated with a slight increased risk of oral cavity cancer, hazard ratio (HR) = 0.81, 95% CI [0.74, 0.89]. However, the risk was driven by smoking status and disappeared among never smokers (Bhaskaran *et al.*, 2014). The study found a heterogenic effect of BMI on different cancer sites, which indicates a different mechanism according to the type of cancer.

As mentioned, the association between BMI and oral cancer is highly controversial and often mediated by both forms of tobacco (smoking and SLT) use. An early study from India found that all forms of tobacco use were associated with a lower BMI (<18.5 kg/m^2; Pednekar *et al.*, 2006). A large population-based prospective study from Bangladesh did not find any relation between BMI and BQ use (most usual form of SLT use in Bangladesh;

Heck *et al.*, 2012). However, BQ is alleged to moderate metabolic signals that control the appetite, resulting in suppressing hunger and increase the risk of malnutrition (Javed *et al.*, 2010). Moreover, a recent study from Bangladesh showed an association of both smoking and SLT with a lower BMI (Mitra *et al.*, 2018). Given the controversy of the relationship between BMI and oral cancer, it is highly likely BMI may play a key role in explaining the relationship between SLT use oral cancer risk in Bangladesh.

Table 13: Previous studies related to oral cancer association with BMI

Autor	Region	Design (case: control)	Gender	Matching	Variables	OR (95%CI)
Radoi *et al.*, (2013)	France	Population-based case-control study (689:3,481)	Male, female	Age, gender	Under-weight (<18.5 kg/m²)	6.25 [3.74-10.45]
					Over-weight 2 years before interview (25 -29.9 kg/m²)	0.53 [0.42-0.68]
Gaudet *et al.*, (2010)	North America Europe South America	Hospital-based case-control (12,716:17,438)	Male, female	Age, gender, ethnicity, neighbourhood	Under-weight ≤ 18.5 kg/m²	2.13 [1.75–2.58]
					Over-weight, >25.0–30.0 kg/m²	0.52 [0.44–0.60]
					Obese, >30 kg/m²	0.43 [0.33–0.57]
Petrick *et al.*, (2014)	North America	Population-based case-control study	Male, female	Age, gender, ethnicity	Whites: Under-weight <18.5 kg/m²	1.48 [0.60-3.65]
					Whites: Obese ≥30 kg/m²	1.34 [1.02-1.76]
					African American <18.5 kg/m²	3.91 [0.72-21.17]
					African American ≥30 kg/m²	0.47 [0.28-0.79]
Kreimer *et al.*, (2006)	Italy, Spain, Poland, Northern Ireland, India, Cuba, Australia, Canada, Sudan (IARC study)	Hospital-based case-control study (1,670:1,732)	Male, female	Age, gender	Low BMI (Never tobacco use)	2.5 [1.6-4.0]
					Medium BMI (never tobacco use)	1.7 [1.1-2.6]
					Low BMI (never used alcohol)	2.6 [2.0-3.5]
					Medium BMI (never used alcohol)	1.5 [1.1-1.9]
Rodriguez *et al.*, (2004)	Italy, Switzerland	Hospital-based case-control study (137:298)	Male, female	Age, gender	BMI ≥ 26.73 kg/m²	0.28 [0.14-0.56]
					BMI 24.22 – 26.72 kg/m²	0.47 [0.24-0.88]
Nieto *et al.*, (2003)	Spain (IARC study)	Hospital-based case-control study (375:375)	Male, female	Age, gender	At diagnosis: ≤22 kg/m²	3.64 [2.72-5.82]
					At diagnosis: 25-23 kg/m²	1.84 [1.22-2.76]
					Two years before: ≤22 kg/m²	3.31 [2.04-5.39]
					Two years before: 25-23 kg/m²	1.65 [1.11-2.47]

2.2.4.6 Diet and nutrition

Dietary deficiency is thought to contribute to 11%–15% of oral cavity cancer cases (Radoi and Luce, 2013). The independent effect of both excessive and deficiencies of several food groups and nutrients were studied extensively in previous studies. A large multicentre case-control study from Italy looked at major dietary patterns, namely animal products, starch-rich, vitamins and fibre, unsaturated fats and retinol and niacin, and their relationship with oral cancer risk (Edefonti *et al.*, 2010). The study results showed that the animal products were positively associated with oral cancer for the highest vs lowest quintile, whereas the starch-rich diet, the vitamins and fibre pattern and the unsaturated fats were inversely associated with oral cancer (see Table 14). An overall diet rich with the animal products and animal fat is associated with an increased risk of oral cancer, whereas a diet rich in fruit, vegetables and vegetables/fats reduced oral cancer risk (Edefonti *et al.*, 2010).

The reduced risk of oral cancer from vegetable- and fruit-rich diets is consistent with previous studies. However, the actual mechanism of the anti-carcinogenic effect of vegetables and fruits is still not clear. The most possible explanation is that many anti-carcinogenic components are found in vegetables and fruits, such as vitamins, fibre, folate, carotenoids and flavonoids. Some of these components are antioxidants and act as a protection against oxidative stress and facilitate DNA repair (IARC, 2012).

Previous studies also demonstrated the protective effect of micro-nutrients against oral cancer. A recent multicentre case-control study from Switzerland and Italy found significant inverse relations between micro-nutrients and oral cancer risk. These included the following: vegetable protein, OR = 0.45, 95% CI [0.29, 0.70], highest vs. lowest quintile; β-carotene, OR = 0.28, 95% CI [0.18, 0.43]; lutein and zeaxanthin, OR = 0.34, 95% CI [0.23, 0.51]; vitamin E, OR = 0.26, 95% CI [0.16, 0.43]; and vitamin C, OR = 0.40, 95% CI [0.25, 0.63]. Additionally, a positive association was reported between saturated fatty acids, animal fat, cholesterol intake and oral cancer risk (see Table 14; Bravi *et al.,* 2013). Overall, when combined with heavy smoking and alcohol drinking, low consumption of fruits and vegetables and high consumption of red meat led to a 10–20-fold excess risk of oral cancer (Bravi *et al.*, 2013).

The oral cancer risk associated with dietary patterns is likely to be higher among smokers and alcohol drinkers. A recent case-control study of 930 oral cancer cases and 2,667 frequency matched controls revealed that less intake of domestic meat (<3 times per week), fish (<3 times per week), seafood (<3 times per week), leafy vegetables (<1 times per day), other vegetables (<1 times per day), fruits (<3 times per week), milk and dairy products (<1 time per week) and eggs (<5 times per week) increased oral cancer risk significantly (Chen *et al.*, 2017b). When stratified by tobacco and alcohol use status, smokers and alcohol drinkers had higher risk compared to non-smokers and non-alcohol drinkers and a significant multiplicative interaction between dietary score, smoking and drinking was found.

Contrary to the possible confounding effect of tobacco and alcohol, some studies did not observe such an effect on oral cancer risk associated with dietary patterns. A large cohort study from the Netherlands found that the consumption of vegetables and fruits were associated with a lower risk of HNC (Maasland *et al.,* 2015). The association was strongest with oral cavity cancer, OR = 0.46, 95% CI [0.27, 0.81], and this association was not modified by cigarette smoking or alcohol drinking status.

Researchers have examined several types of diets by region and their relationship with oral cancer risk. The Mediterranean diet, typically from Italy, Southern France, Greece, Spain and Morocco and characterised by frequent consumption of mixed vegetables and fruit, cereals, fish and seafood, olive oil, moderate alcohol consumption and relatively low consumption of meat and dairy products, showed a decreased risk of oral cancer from regular intake (Filomeno *et al.,* 2014). The study findings showed that an increasing level of the Mediterranean diet was associated with a lower risk of oral and pharyngeal cancer. The odds ratio for subjects scoring six or higher on the Mediterranean diet score compared with two or less was 0.20 (95% CI [0.14-0.28]; see Table 14; Filomeno *et al.*, 2014).

Evidence is limited concerning oral cancer risk related to the South-Asian diet. In general, the South-Asian diet is characterised by spicy food, curry, vegetables, fish, rice, grains and meat. However, the diversity of diet across the region and within the country requires extensive research to look at the risk of oral cancer from different forms of the diet. The majority of previous studies related to diet and oral cancer risk are from India. A large percentage of Indians, particularly Hindus, are vegetarian and avoid meat and fish. A lower risk of oral cancer was observed among vegetarians compared to non-vegetarians in India (Gupta *et al.,* 2012). Nevertheless, traditionally, rural residents of India consume a high amount of ghee (clarified butter with a high content of saturated fat), which is likely to increase oral cancer risk (Hebert *et al.,* 2002). A recent case-control study from India reported a protective effect of eating yellow vegetables (carrot, pumpkin, sweet potatoes and corn), cruciferous vegetables and citrus fruits once a week (Gupta *et al.*, 2017). In addition, an increased risk of oral cancer was observed for individuals who consumed red meat and very spicy food more than once a week (see Table 14). Gupta and colleagues also reported a higher risk of oral cancer from drinking very hot tea, OR = 3.19, 95% CI [1.99, 5.11], and a similar finding was reported in a case-control study from Southern India (Rajkumar *et al.*, 2003). However, Rajkumar *et al.,* (2003) found that the higher risk of oral cancer from a low intake of vegetables was higher among smokers, indicating the residual effect of tobacco.

Table 14: Previous case-control studies related to oral cancer risk and diet

Autor	Region	Design (case: control)	Gender	Matching	Dietary factors	OR (95% CI)
Chen *et al.*, (2017b)	China	Hospital-based case-control study (930:2,667)	Male, female	Age, gender	Leafy vegetables <1 per day	3.91 (2.98–5.14)
					Fruits < 3 times per week	3.00 (2.53–3.56)
					Lowest dietary score (smokers)	7.32 (4.59-11.68)
					Lowest dietary score (alcohol)	6.93 (3.92–12.26)
Bravi *et al.*, (2013)	Italy, Switzerland	Hospital-based case-control study (768:2,078)	Male, female	Age, gender	All vegetables	0.19 (0.13–0.29)
					All fruits	0.39 (0.26–0.59)
					Animal fat	2.47 (1.71–3.57)
					Vegetable fat	0.54 (0.37–0.78)
					Red meat	1.55 (1.04–2.31)
Filomeno *et al.*, (2014)	Italy, Switzerland	Hospital-based case-control study (768:2,078)	Male, female	Age, gender	[a]MDS 0-2	1.0
					MDS 3	0.46 (0.33–0.65)
					MDS 4	0.45 (0.32–0.63)
					MDS 5	0.26 (0.18-0.28)
					MDS 6-9	0.20 (0.14-0.28)
Bosetti *et al.*, (2003)	Italy	Multicentre Hospital-based case-control study (1,362:3,322)	Male, female	Age, gender, study centre	MDS <3	0.52 (0.38–0.71)
					MDS 3	0.41 (0.30–0.57)
					MDS 4	0.35 (0.24–0.50)
					MDS 5	0.40(0.26–0.62)
					MDS ≥ 6	0.77 (0.71–0.83)
Gupta *et al.*, (2017)	India	Hospital-based case-control study (187:240)	Male, female	Age, gender	Yellow veg (> once a week)	0.23 (0.13–0.38)
					Cruciferous veg (> once a week)	0.37 (0.23–0.60)
					Citrus fruits (> once a week)	0.49 (0.30–0.80)
					Red meat (> once a week)	2.34 (1.34–4.09)
					Very spicy food	1.79 (1.12–2.87)
					Very hot tea	3.19 (1.99–5.11)

Autor	Region	Design (case: control)	Gender	Matching	Dietary factors	OR (95% CI)
Rajkumar *et al.*, (2003)	Southern India	Hospital-based case-control study (187:240)	Male, female	Age, gender	Red meat ≥2 in a week	1.54 (1.00-2.37)
					Ham ≥2 in a week	4.40 (2.88-6.71)
Edefonti *et al.*, (2010)	Italy	Multicentre Hospital-based case-control study (804:2,080)	Male, female	Age, gender, study centre	Animal Products (high vs low quantile)	1.56 (1.13–2.15)
					Starch-rich (high vs low quantile)	0.71 (0.50– 0.99)
					Veg and fibre (high vs low quantile)	0.47 (0.34–0.65)
					Unsaturated fat (high vs low quantile)	0.63 (0.45–0.86)

[a] *MDS (Mediterranean diet score)*

2.2.4.7 Family history of cancer

Previously, little attention was paid to the possible association of a family history of cancer and oral cancer risk. However, several case-control studies stated that a family history of cancer might be a risk factor for oral cancer. The ICARE study, a large population-based case-control study (689 cases: 3,481 controls) from France reported that a history of HNC among first-degree relatives is associated with an increased risk of oral cancer, OR =1.9, 95%CI [1.2, 2.8]. Additionally, this risk was higher among subjects who smoke, OR = 2.7, 95% CI [1.8, 3.4], drink alcohol, OR = 2.6, 95% CI [1.2, 3.3], and had first-degree relatives with HNC (Radoi *et al.*, 2013b). In the same vein, a large case-control study from Italy and Switzerland reported an increased risk of oral and pharyngeal cancer among subjects whose first-degree relative had a history of laryngeal cancer (Turati *et al.*, 2013).

The increased risk of oral cancer based upon a family history of cancer could be due to shared environmental exposure to the established risk factor, such as tobacco and alcohol. However, a previous study showed the risk of oral and pharyngeal cancer increased moderately with a family history of lung cancer and was not associated with a family history of cancer associated with alcohol and tobacco use, for example, liver or oesophagus cancer (Pelucchi *et al.*, 2006). Hence, such findings suggest that tobacco and alcohol use cannot explain the association between increased risk of oral cancer and a family history of cancer. However, this claim had been strongly opposed by Brown *et al.,* (2001) who showed the risk of oral cavity cancer increased for subjects whose first-degree relatives had a history of oral cavity cancer, OR = 2.5, 95% CI [0.80, 8.00], and UADT (Upper aerodigestive tract) carcinoma, OR = 2.6, 95% CI [1.4, 4.8].

An elevated risk of oral cancer based upon a family history of UADT cancer is higher among subjects with conventional risk factors, such as tobacco and alcohol use and infrequent intake of vegetables and fruits. The highest risk was observed among subjects who were heavy drinkers and smokers and with a family history of UADT cancer, OR = 60.4, 95% CI [21.0, 174.0] (Brown *et al.*, 2001). In line with this finding, an early study by Goldstein *et al.,* (1994) found that increased risk of oral cancer is attributable to environmental factors (tobacco, alcohol) and increased risk of oral cancer was associated a family history of smoking-related cancer among male but not female relatives. This inconsistency of the effect of tobacco and alcohol in relation to a familial history of cancer and oral cancer risk was further clarified by Gravello *et al.*, (2008). The researchers found that a history of oral and pharyngeal cancer and laryngeal cancer among family members were strong predictors of the risk of oral and pharyngeal cancer and independent from tobacco and alcohol. For the non-smokers and non-drinkers with a family history of oral and pharyngeal cancer, their odds ratio was 1.9 (95% CI [0.80, 4.5]). However, the risk was subsequently higher among subjects whose first-degree relatives had a history of oral and pharyngeal cancer and the subjects were heavy smokers and drinkers (OR = 42.5, 95% CI [18.2, 99.8]; Garavello *et al.,* 2008). Therefore, a familial aggression of oral cancer is most likely attributed to a family history of oral, pharyngeal and laryngeal cancer and the risk is subsequently higher among subjects with a history of smoking and alcohol drinking and a lower intake of vegetables and fruits.

2.2.4.8 Viral infection

The aetiology of oral cancer is complex and involves many factors. Most cited established risk factors are SLT, smoking and alcohol consumption (IARC, 2012). However, many subjects develop oral cancer without exposure to these significant risk factors, thereby emphasising the role of oral hygiene factors, genetic susceptibility and oncogenic viruses. Concerning viruses, although the relationship between HPV and oral cancer has been studied extensively, findings have been inconsistent and contradictory.

A large multicentre hospital-based case-control study from Canada with 460 incident cases and 458 frequency matched controls showed that HPV infection was present in 41.2% cases of oral cancer compared to 14.5% of controls. HPV 16 was the most predominant genotype and presented in 6.9% oral cancer cases and was associated with a three-fold increased risk of oral cavity cancer, OR = 3.43, 95% CI [1.01, 11.66]. Nevertheless, this risk was higher for oropharyngeal cancer compared to oral cavity cancer, OR = 47.23, 95% CI [23.10, 96.57] (Laprise *et al.*, 2017).

Several studies among young adults without other traditional risk factors (tobacco and alcohol) showed high-risk HPV was not associated with oral squamous cell carcinoma. For instance, a study among young adults with no history of smoking and alcohol drinking showed that only one case (1.3%) had a positive HPV result (Poling *et al.*, 2014). This is consistent with studies conducted by Braakhuis *et al.,* (2014) and Bragelmann *et al.,* (2013), who did not find any trace of HPV infection among young oral cancer patients (non-smokers and non-drinkers).

To examine the possible risk of oral cancer from HPV, the IARC conducted a multicentre hospital-based case-control study in nine countries: Italy, Spain, Northern Ireland, Poland, India, Cuba, Canada, Australia and Sudan (Herrero *et al.*, 2003). Results showed HPV DNA was detected in only 3.9% of 766 oral cancer cases compared to 18.3% of oropharyngeal cases and HPV 16 genotype was the most common type found in HPV-positive case patients. Additionally, the presence of HPV DNA was common among non-smokers, non-chewers and non-drinkers compared to smokers, chewers and drinkers and more common among cases who had more than one sexual partner and practised oral sex, suggesting sexual transmission.

Some studies suggested a stronger association between HPV and tonsillar cancer compared with other subsites for oral cancer. In light of this, a case-control study from Canada confirmed the independent association between HPV infection and oral cancer and found that the association was stronger in tonsil-related cancer compared to other types of oral cancer (Pintos *et al.*, 2008). After adjustment for age, sex, schooling, race, religion, language, tobacco smoking and alcohol drinking the odds ratios of HPV infection were 19.32 (95% CI [2.3, 159.5]) for tonsil-related cancer and 2.14 (95% CI [0.4, 13.0]) for non-tonsillar oral cancer (Pintos *et al.*, 2008).

Although findings have mostly been confirmatory and the aetiological role of HPV infection in oral cancer is well documented, this role varies widely among different subsites of cancer, genders and geographical regions. A large case-control study from Kerala, South-India did not find any HPV infection among oral cancer patients and controls (Laprise *et al.*, 2016). Studies from another part of India (Gujrat and Mumbai) also reported the absence of HPV infection among oral cancer patients (Pathare *et al.*, 2011; Patel *et al.,* 2014). Safer sexual behaviour that may stem from religious norms in India may have contributed to this null finding, as the study from South-India reported that nearly 90% of oral cancer patients and controls had only one-lifetime sexual partner, suggesting that risky sexual behaviour is low and this explains the lower transmission of HPV infections.

Findings from studies conducted in Bangladesh on HPV-related oral cancer are contradictory. Only two comprehensive studies have examined the possible presence of HPV infection among oral cancer patients. One study, a case-series analysis of 34 oral cancer patients, looked at the presence of high-risk HPV genotypes (HPV 16 and HPV 18; Akther *et al.*, 2013). The study results suggested HPV infection among Bangladeshi oral cancer patients was near absent (only one specimen was HPV-positive). However, a more recent study conducted by Shaikh *et al.,* (2017) revealed that out of 55 oral cancer patients, 11 (31%) cases were HPV-positive. Further, the result showed the same trend as other Western country studies: HPV infection was more common in cancer of the oropharynx and HPV 16 was the predominant genotype (Shaikh *et al.*, 2017).

2.2.5 Smokeless tobacco use and oral cavity cancer

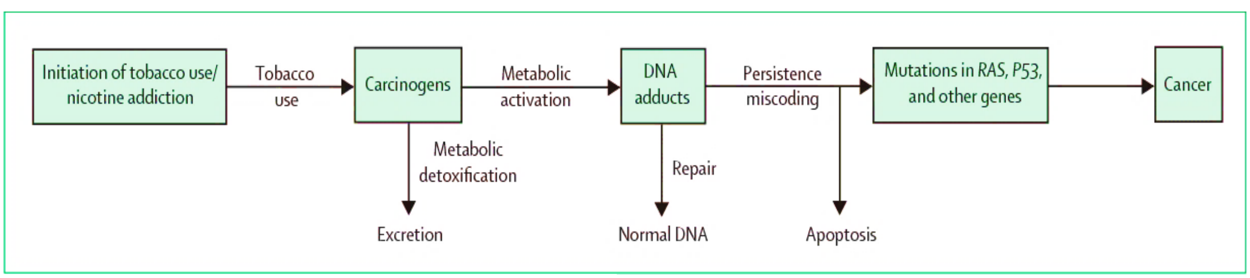
2.2.5.1 Biochemical mechanism of oral carcinogenicity of smokeless tobacco

More than 30 types of carcinogens exist in SLT, including TSNAs, nitrosoamino acids, polycyclic aromatic hydrocarbons, aldehydes and other metals (IARC, 2008). Using SLT is the highest known non-occupational human exposure to nitrosamine and is 100–1,000 times higher than exposure from regular foods and beverages. According to IARC monograms, every gram of commonly known SLT contains 1–5 µg of NNK and NNN, two recognised human carcinogens. In a comprehensive study, Stepanov *et al.*, (2005) identified the carcinogens in SLT from Indian subcontinents. They looked at the level of four tobacco-specific nitrosamines: NNN, N-nitrosoanatabine, N-nitrosoanabasine and NNK. The highest level of TSNAs was observed among different brands of zarda and khaini. The concentration of NNN and NNK in these products ranged from 1.74–76.9 and 0.08–28.4 ųg/g, respectively (Stepanov *et al.*, 2005). Zarda is also the most common type of SLT product used in Bangladesh (Huque *et al.,* 2018).

The amount of NNN and NNK uptake in humans is determined by the detection of these carcinogens in one's urine. According to Belinsky *et al.,* (1990), 20 years of continuous SLT use exposes an individual to 75–150 mg, or about 1.5 mg/kg bodyweight, of NNK, similar to the amount causing tumours in rats (1.8 mg/kg body weight), in addition to substantial exposure to NNN. The target tissue of cancer among SLT users resembles those seen in rats exposed to NNK and NNN (Bofetta *et al.*, 2008).

Several authors have suggested the mechanism of carcinogenicity of SLT. One of the most cited studies is that of Bofetta *et al.,* (2008), which was adapted from Hecht (1999). Befetta *et al.* mentioned that people start using SLT at an early age because of peer pressure and the extensive marketing strategies of tobacco companies, and over time they become addicted to nicotine and cannot give up SLT. Nicotine is not carcinogenic, but every portion of SLT contains 30 different types of carcinogens with a high amount of NNK and NNN. All SLT users take up these carcinogens and ingest them into their bodies. This process triggers the metabolic activation of carcinogens and the formation of DNA adducts, which are carcinogenic metabolites bound covalent to DNA. In the next stage after subsequent mutations, they may ultimately lead to oral cancer (see Figure 8)

Figure 8: Conceptual model of smokeless tobacco carcinogenesis. Source: Bofetta *et al.,* (2008).



2.2.5.2 Epidemiological evidence of oral cancer from smokeless tobacco use

Evidence from Europe and America

The risk of having oral cancer from SLT use varies extensively worldwide. Available evidence from different epidemiological studies in the United States and Europe support a weak but causal relationship between SLT use and oral cancer. A comprehensive meta-analysis of 32 epidemiological studies concluded a minor increased risk of oral cancer resulted from SLT use, with a pooled odds ratio 1.87 (95% CI [1.40, 2.48]; Weitkunat *et al.*, 2007). However, findings from American studies related to SLT use and oral cancer are inconsistent with imprecise estimations with limited control with smoking. While adjusting for smoking status, a recent review among American studies found strong association between ever tobacco chewing and oral cancer (OR = 1.81, 95% CI [1.04, 3.17]; Wyss *et al.*, 2016).

Contrary to the American studies, Scandinavian studies did not observe an increased oral cancer risk among snus users. A large cohort study among 125,576 non-smoking Swedish males reported an increased risk of pancreatic cancer in never-smoking snus users, RR = 2, 95% CI [1.2, 3.3], compared with never users of any tobacco but unrelated to the incidence of oral cancer, RR = 0.80, 95% CI [0.4, 1.7], (Luo *et al.*, 2007). Similar findings were reported in a large cohort study among 10,136 Norwegian men, in that the risk of having oral and pharyngeal cancer among snus user compared to non-users was minimal, RR = 1.10, 95% CI [0.50, 2.41], (Boffetta *et al.*, 2005). A possible explanation of this estimate in the Scandinavian country could be the new standard of snus manufacturing and storage adopted in the late 1990s (NCI and CDC, 2014). Therefore, the effects of long-term exposure to this new snus are still unknown.

Evidence from the African region

In general, limited data are available related the adverse effects of SLT use on oral health in the African region. Since 1990, no large population-based study has been conducted on oral cancer incidence among South Africans (NCI and CDC, 2014). However, few studies have been conducted in the North African region, namely in Sudan. An early retrospective study among 3,670 Sudanese indicated that toombak (oral snuff, known locally as toombak, homemade from finely ground leaves of tobacco) users are seven times more likely to have oral cancer compared to non-users and that risk can increase by 11-fold among long-term users (Idris *et al.,* 1995). A previous review of 33 studies from Sudan concluded that toombak use plays a key role in causing oral cancer in Sudan because of its potent carcinogenicity and synergistic factors that enhance the carcinogenesis of other risk factors, such as smoking (Ahmed, 2013). However, the gender specificity of oral cancer from toombak use was opposite to the South-Asian region, where men had a higher frequency of oral cancer compared to women. Notably, 95% of toombak users in Sudan are male and female use is considered a social stigma (Ahmed, 2013).

Evidence from Eastern Mediterranean countries

The locally produced SLT product known as shammah (made from the mixture of tobacco powder, slaked lime, ash, oil, black pepper and other flavouring agents) is widely consumed in the Eastern Mediterranean region, such as Yemen and Saudi Arabia (Bakdash, 2017). Most studies from Arab countries focused on oral cancer risk from shammah use. A recent pooled analysis of studies from the Middle East and North Africa showed that the odds of developing oral cancer among shammah users was nearly 39 times higher compared to the non-users, OR = 38.74, 95% CI [19.50, 76.96] (Quadri, Tadakamadla and John, 2019). A previous case-control study from Yemen demonstrated shammah was a major risk factor of oral cancer (see Table 15; Nasher *et al.*, 2014). Another hospital-based retrospective study in Yemen found that 76.1% of oral cancer patients had a history of using shammah (Sawair *et al.*, 2007).

Frequent use of shammah also was attributed to a higher incidence of oral cancer in the KSA (Kingdom of Saudi Arabia). Oral cancer is the third-most common malignancy in the KSA and is associated with 89% of oral cancer cases (Alsanosy, 2014). A previous case-control study from the KSA concluded that shammah use increases oral cancer risk substantially, OR = 29.30, 95% CI [10.33, 83.13] (see Table 15; Quadri *et al.*, 2015).

Evidence from South-East Asia

The risk of oral cancer from SLT use has been studied extensively in SEAR. Compared with studies from Europe and America, studies from the South-Asian region reported a higher risk of oral cancer associated with SLT use. This variation of oral cancer risk estimates from other regions can partly be explained by the chemical contents of different SLT products, particularly TSNAs and their usage (Gupta *et al.,* 2018).

A review of 37 studies from six WHO regions reported that the highest risk of oral cancer of SLT was observed in the SEAR, OR = 4.44, 95% CI [3.51, 5.61], and the risk was higher among women, OR = 5.83, 95% CI [2.93, 11.58]. Additionally, using gutkha, OR = 8.67, 95% CI [3.59, 20.93], and betel liquid, OR = 7.18, 95% CI, [5.48, 9.41], showed the highest oral cancer risk in this region (Asthana *et al.*, 2018). In another meta-analysis of South-Asian studies, higher oral cancer risk in this region was associated with BQ use OR= 7.1, 95% CI [4.5-11.1] and odds were higher among women than men, men odds ranged between 1.2 to 5.8 and among women 6.4 to 25.3 (Khan, Tönnies and Müller, 2014)

A recent hospital-based case-control study from India reported an eight-fold increase risk of oral cancer among ever SLT users compared to never user, OR = 8.51, 95% CI [4.90, 14.77] (Gupta *et al.*, 2017). The association between SLT use and oral cancer risk in India also showed a gender difference. A recent review of Indian studies by Sinha *et al.,* (2016) showed women in India had a higher risk of developing oral cancer from SLT use compared to men (OR = 12 vs. 5.20). Interestingly, SLT use is higher among men than women in India (29.6% vs 12.8%: WHO, 2018b). Similar oral cancer risk was observed in Pakistan, where women had a 29-fold increased risk of mouth cancer from SLT use compared to 21-fold in men (Khan *et al.*, 2017).

Although many studies from neighbouring countries, such as India and Pakistan, examined the risk of developing oral cavity cancer from SLT use, a study has yet to be conducted to establish the risk factors of oral cancer in Bangladesh. As mentioned in Chapter 1, Bangladesh is the home to more than 22 million SLT users (WHO, 2017). Therefore, the burden of oral cancer related to SLT use is expected to be substantial. Also, the type and chemical content of SLT varies extensively among countries and even within countries, making the generalisability of study findings from other neighbouring countries problematic in the Bangladeshi context (NCI and CDC, 2014).

Patterns of smokeless tobacco use and its association with oral cancer

Previous studies have emphasised the dose-response relationship between SLT and oral cancer incidence, with a higher frequency and longer duration of SLT use being associated with an increased risk of oral cancer. A recent study in India demonstrated a linear dose-response association between oral cancer and SLT use for age at initiation, total duration of use and frequency of chewing per day (p <.001; Gupta *et al.*, 2017; see Table 15). When compared with never users, the risk of oral cancer for those who started using SLT at the age of 15 years or younger was 11-fold and decreased to just over 2-fold for those who started at age 20 years or older. Similarly, for duration of chewing, the risk of oral cancer increased by five-fold for those who used SLT for 10 years or fewer and increased to more than double for those who used SLT for more than 40 years. Also, the risk of oral cancer increased by 2-fold for those who chewed SLT 1–5 times per day to nearly 42-fold for those who chewed more than ten times a day (Gupta *et al.,* 2017).

Similar to the Indian study, a case-control study from Pakistan reported a dose-response relationship between SLT and oral cancer (Khan *et al.,* 2017). The study findings showed that 1–10 pack-years of naswar use is associated with a 12-fold increased risk of oral cancer and for 20-pack-years, the risk increased to nearly 30-fold (see Table 15). However, this finding should be interpreted with caution due to a large variance in the reported confidence intervals. Contrary to the studies from South-Asia, a case-control study from New England did not observe a statistically significant association between lifetime duration of SLT use and oral cancer risk (p =.19). Moreover, a non-significant association was also reported for an average frequency of SLT per week (p =0.61; Zhou *et al.*, 2013).

In Bangladesh, the dose-response relationship between SLT use and oral cancer has yet to be investigated. However, a recent case-control study by Rahman *et al.*, (2012) examining the association between coronary heart disease and SLT use revealed that mean duration of SLT use was highest among sadapata users (28 years; range = 3–60 years) followed by gul users (17 years; range = 0.5–45 years) and zarda users (16 years; range = 0.1–55 years). A similar intensity was reported in another study: 57.7% of zarda, 6% of sadapata and 6.4% of gul users were heavy users (used at least once per day). Moreover, among current SLT users, 37.1% of zarda, 5% of sadapata and 4% of gul users used the products for over 10 years (Rahman *et al.*, 2015). A previous GATS report from Bangladesh (2009) demonstrated that just over one-third of current users (37%) used SLT products 5–9 times a day and 30.9% used it less than five times a day. Given the intensity and long duration of SLT use in Bangladesh, the dose-response relationship between SLT use and risk of oral cancer is expected to be significant.

Betel quid chewing and oral cancer risk

Globally, after the tobacco, alcohol and caffeine consumption, BQ chewing is the fourth-most popular psychoactive habit and used by 600 million people around the world (Chen *et al.*, 2017). It is a masticatory mixture and the preparation varies widely around the world. However, areca nut (betel nut), slaked lime (calcium oxide and calcium hydroxide) and a leaf of piper betel leaf are the key components with other sweetening and flavouring ingredients added. In South-Asia, tobacco is added with BQ, mostly in Bangladesh, India and Pakistan. However, it has never been added in other BQ using countries including China, Taiwan and Papua New Guinea (IARC, 2004). Based on the available evidence, the IARC (1985) classified BQ with or without tobacco as Group I carcinogens to humans and reported an elevated risk of oral cancer.

Majorities of the studies that explored the association between BQ chewing and oral cancer risk were from India. There were few from Pakistan and pacific region. Although a variety of ingredients are added to BQ according to local preference, existing studies have not offered a distinct evaluation of each ingredient. Based on available results, the only conceivable difference is whether tobacco is added with BQ (Radoi and Luce, 2013).

The association between BQ chewing and oral cancer risk was first reported in 1933 and was based on study of 100 oral cancer patients from India (Thomas and Kearsley, 1933). In Asia, the risk of oral cancer from BQ chewing with or without tobacco appeared to be stronger than smoking or drinking alcohol. A previous meta-analysis of 50 publications showed that the risk of oral cancer from BQ without tobacco in South-Asia was 2.56 (95% CI [2.00, 3.28]; 15 studies) and 7.74 (95% CI [5.38, 11.13]; 31 studies) for BQ with tobacco (Guha *et al.*, 2014). In another hospital-based case-control study from Southern India, also known as the HNC (HeNCe) Life Study, found that 72.5% cases and 17.5% controls used SLT. The study concluded that BQ chewers were 11-times more likely to develop oral cancer compared to non-users and the significance remained after adjusting for other confounders (see Table 15; Madathil *et al.,* 2016). However, this study failed to characterise, whether tobacco was added with the BQ or not. Also, former BQ chewers had shown higher risk of developing oral cancer (12-fold) than current users (11-fold), suggesting reverse causality.

Similar to Indian study, a multicentre case-control study from Karachi, Pakistan also found a significant association between oral cancer and BQ chewing (Merchant *et al.*, 2000). After adjusting for the confounders, the odds of oral cancer among BQ with tobacco chewers was 9.9 (95%CI: 1.76, 55.62) and those using BQ without tobacco was 8.4 (95%CI: 2.31, 30.64). However, these estimates were not precise as with large confidence interval (see Table 15; Merchant *et al.*, 2000).

The increased risk of oral cancer associated with BQ without tobacco is likely to be associated with one of the key ingredients: areca or betel nut. Areca nut is the seed of the oriental palm, also known as areca catechu, and is widely used as the basic ingredient of BQ, used with other SLT products or used alone. Based on epidemiological studies, the IARC (2004) defined areca or betel nut as Class-I carcinogens to humans. In most South-Asian countries, areca nut is used in BQ with tobacco, which makes it more difficult to determine the effect of areca nut alone because adding tobacco to BQ acts as a confounder (Warnakulasuriya, Trivedy and Peters, 2002).

Countries, such as Taiwan, where tobacco is not added to BQ provide a better indication of the carcinogenicity of areca nut. A hospital-based case-control study among Taiwanese males reported a strong positive association between BQ without tobacco and oral cancer risk, OR = 6.31, 95% CI [3.98, 10.00], and for BQ with betel inflorescence OR = 6.72, 95% CI [3.38, 12.99] (Wu *et al.*, 2016). Similar findings were reported in Papua New Guinea, where tobacco is not added to BQ and chewing BQ was associated with a more than two-fold increased risk of oral cancer, OR = 2.47, CI 95% [1.13, 5.40] (Thomas *et al.,* 2007). The high-risk among Taiwanese men is likely to be the synergistic effect of betel nut and smoking, as 90% of Taiwanese betel nut chewers are also smokers (Wen *et al.*, 2010).

In contrast, several studies observed a non-significant or only moderately significant association between chewing BQ without tobacco and oral cancer incidence. A previous case-control study by Muwonge *et al.,* (2008) found a weak or borderline association between BQ chewing without tobacco and oral cancer incidence. Similarly, Dikshit and Kanhere (2000) found that tobacco chewers had a six-fold increased oral cancer risk. Notably, although non-tobacco chewers also had an increased risk, the association was not statistically significant. These results need to be interpreted with caution as the sample only included 16 subjects who chewed BQ without tobacco. Hence, the estimation may not be precise.

Among all HNC subsites (oral cavity, oropharynx, hypopharynx and larynx), oral cavity appeared to be at the highest risk of developing cancer from BQ chewing. An extensive case-control study from East Asia including eight centres revealed that the risk of developing cancer from BQ chewing was highest in the oral cavity, OR = 18.5, followed by the larynx (OR = 5.87) and oropharynx (OR = 5.47; Lee *et al.*, 2018).

Gender difference was observed for oral cancer risk assoctiated with BQ chewing and the risk was higher among women, a finding supported by Guha *et al.*, (2014) in their meta-analysis. Thet study reported a higher risk of orla cancer for women, mmR = 23.06, 95% CI [5.94, 89.58], than men, mmR = 4.92, 95% CI [3.88, 6.24]. Moreover, they found BQ chewing to be responsible for 63.2% of all oral cancer cases among women (PAF%; attributable cases). The gender difference of oral cancer risk associated with BQ chewing was also mentioned in the case-control study by Muwonge *et al.*, (2008), who found women had higher risk than men (for BQ without tobacco, OR = 5.4 vs OR = 3.3, respectively: for BQ with tobacco, OR = 11.8 vs OR = 3.4, respectively).

A linear dose-response relationship was observed between amount of BQ chewed per day and total duration of use. A comprehensive systematic review of case-control and cohort studies from the South-Asian region demonstrated that odds of oral cancer for chewing five quids a day was 3.3 and this increased to 24.7 for those chewing 10 quids a day. Additionally, the odds of developing oral cancer for BQ chewing for 10 years was 3.4 and increased to 14.6 for those chewing for 20 years (Awan and Patil, 2016). Similarly, a multicentre case-control study from India found that 19 years of BQ chewing increased oral cancer risk by three-fold and it increased by five-fold for those chewing 40 years or more. Further, chewing BQ five or more times per day showed an 11-fold increased risk of oral cancer compared to two-fold for 1–3 quids per day (Znaor *et al.*, 2003).

Starting BQ from an early age also increased oral cancer risk. In an early study investigating the role of BQ chewing in developing oral cancer, BQ chewing at an early age was associated with a five-fold elevated risk in women but was statistically insignificant among men (Balaram *et al.*, 2002). The possible effect of quitting BQ was reported in several studies, but the result was inconclusive, as Balaram *et al.*, (2002) did not find any clear decline of oral cancer risk after quitting BQ. However, Znaor *et al.*, (2003) found that quitting for more than 10 years showed a significant reduction of oral cancer risk.

In Bangladesh, BQ is usually chewed with tobacco. The majority BQ users in Bangladesh use tobacco. A large cohort study among 202,874 Bangladeshi adults showed that 80.4% of ever chewers chewed BQ with tobacco (Fen Wu *et al.*, 2015). Two of the most popular varieties are zarda and sadapata. Sadapata is more popular among rural women. A previous cross-sectional from Bangladesh showed that 68% of the women used sadapata and were three times more likely to be sadapata users compared to men. An opposite scenario was observed for zarda, men were three times more likely to use zarda compared to women (*p* <.001; Mia *et al.*, 2017). Yet, no study from Bangladesh reported the risk of oral cancer associated with BQ chewing.

2.2.5.3 Population attributable risks of oral cancer for smokeless tobacco use

The population attributable fraction (PAF) is a useful tool to understand the burden of risk factors in specific cancer incidences (Radoi *et al.,* 2015). In an extensive review, Petti (2009) revealed that 25% of oral cancer cases worldwide are attributable to tobacco use (both smoked and/or SLT), 7%–9% to alcohol drinking and more than 50% to BQ chewing. Although several epidemiological studies have examined the joint effects of tobacco and alcohol drinking, and found interaction on an additive (Hashibe *et al.,* 2009; Anantharaman *et al.,* 2011) or multiplicative scale (Garrote *et al.,* 2001), few have examined the proportion of oral cancer that can be attributable to SLT consumption alone, smoking alone and their combined effects. Understanding the independent and joint effects of different tobacco product consumption would have important implications for prevention.

A matched-case-control study from Pakistan found that the overall PAF of the commonly used SLT naswar for oral cancer in Pakistan was 59% and 68% of male oral cancer cases and 38% of female oral cancer cases were attributable to naswar use. The total number of incidence cases of oral cancer in Pakistan attributable to naswar use was 9,094 of 15,414 incident oral cancer cases in Pakistan (Khan *et al.,* 2017). A similar risk was observed in a case-control study from India that found 66.1% of oral cancer cases were attributable to SLT chewing and 84.4% for dual use of smoking and SLT (Dikshit and Kanhere, 2000). The gender difference in PAF is also apparent from another Indian study, which reported that PAF for individuals who ever chewed SLT was 42.6% for males and 81.2% for females and the PAF for ever smoked and ever SLT use was 58.0% among males (Muwonge *et al.,* 2008). Balaram *et al.,* (2000) also observed similar a gender difference of PAF for oral cancer, with 68% of oral cancer cancers among men and 87% of cases among women being attributable to the joint effect of smoking and tobacco chewing. Hence, these findings highlight that a high prevalence of female SLT use and high prevalence of dual use of smoked tobacco and SLT among males largely explains oral cancer incidences in India.

The attributable risk of oral cancer from SLT use differs between South- and East-Asian countries. As mentioned, tobacco is not added to BQ in East Asia; therefore, a lower attributable risk of oral cancer was reported in case-control studies in the East-Asian region. A recent case-control study among an East-Asian population reported that PAF for oral cancer of ever BQ chewing among the Taiwanese and Chinese population was 33%, 2.8% for tobacco alone and 31.4% for alcohol drinking. However, due to a lack of statistical power, the study failed to report the combined effect of two risk factors (Lee *et al.,* 2019). In comparison, the PAR (Population attributable risk) for oral cancer in Europe are mostly attributable to tobacco smoking and alcohol drinking. A population-based case-control study from France showed that PAR for oral cavity cancer were 78.6% for tobacco smoking and 7.3% for alcohol drinking (Radoi *et al.,* 2013).

Table 15: Previous case-control studies related to oral cancer risk from smokeless tobacco use

Authors	Region	Design (case: control)	Gender	Matching	Variables	OR (95% CI)
Idris *et al.,* (1995)	Sudan	case-control study (646:2,820)	Male and female	Age, gender	Short-term use of Toombak	7.3 [4.3–12.4]
					Long-term use of Toombak	11.0 [4.8-25.1]
Nasher *et al.*, (2014)	Yemen	Hospital-based case-control (60:120)	Male and female	Age, gender	Shammah use alone	149.5 [12.3–1812]
					Shammah and qat chewing	43.1 [7.0–266]
					Shammah, qat chewing, smoking	14.2 [2.9–69.0]
Quadri *et al.,* (2015)	Saudi Arabi	Hospital-based case-control (48:96)	Male and female	Age, gender, location	Shammah	29.3 [10.3–83.1]
					Cigarettes smoke	6.74 [2.18-20.8]]
Gupta *et al.,* (2017)	India	Hospital-based case-control study (187:240)	Male and female	Age, gender	Ever chewing tobacco use	8.52 [4.90-14.77]
					Duration of chewing >41 years	11.7 [5.37-23.24]
					Age of initiation	2.62 [1.25–5.48]
					Frequency of chewing per day >10	41.87 [19.61-89.40]
Khan *et al.*, (2017)	Pakistan	Hospital-based case-control study	Male and Female	Age, gender	Ever Naswar use	22.9 [9.4-57.4]
					Current Naswar use	28.7 [10.5-74.0]
					Past Naswar use	16.4 [4.9-41.2]
					Naswar pack-year >20	28.3 [9.30 -86.2]
					Naswar dip duration >10 minutes	142.2 [31.1-650.5]
Merchant *et al.*, (2000)	Pakistan	Hospital-based case-control study (79:149)	Male and Female	Age, gender	Ever used Naswar	9.53 [1.73–52.5]
					Ever used pan with tobacco	8.42 [2.30 –30.6]
					Ever used pan without tobacco	9.90 [1.76 – 55.6]
Thomas *et al.*, (2007)	Papua New Guinea	Hospital-based case-control study (143:477)	Male and female	Age, gender, location	Betel chewing	2.03 [1.01-4.09]
					Current heavy betel chewers	2.47 [1.13-5.40]
					Smoking and betel chewing	4.85 [1.10-22.25]

Authors	Region	Design (case: control)	Gender	Matching	Variables	OR (95%CI)
Zhou *et al.*, (2013)	America	Population-based case-control (1,046:1,239)	Male and Female	Age, gender, location	SLT use ≥20	1.20 [0.67-2.16]
					Lifetime duration of SLT use ≥10	4.06 [1.31-12.64]
					Frequency per week ≥14	1.39 [0.39-4.89]
Amtha *et al.*, (2014)	Indonesia	Hospital-based case-control study (81:162)	Male and female	Age, gender	BQ chewers	4.59 [1.11-18.91]
					No of BQ per day (1-10)	5.97 [1.08-33.04]
					Duration of years	3.99 [0.90-17.58]
					Type of BQ (betel leaf + areca nut + lime + tobacco)	4.74 [1.13-19.89]
Madathil *et al.,* (2016)	India	Hospital-based case-control study (350:371)	Male and female	Age, gender	Current BQ chewers	11.3 [6.72 -19.05]
					Former BQ chewers	12.1 [6.98-21.02]
					> 260 lifetime chew-years	22.52 [11.87-42.71]
					One BQ per day for one year	3.92 [1.87-8.21]
Znaor *et al.*, (2003)	India	case-control study (1,563:3,638)	Male	None	Chewing without tobacco	2.19 [1.63-2.95]
					Chewing with tobacco	5.05 [4.26-5.97]
					Duration of chewing ≥40 years	5.19 [3.70-7.29]
					More than 5 BQ per day	11.94 [8.93-15.06]
					Time since quitting (10-14 years)	0.71 [0.37-1.35]

2.2.6 Theoretical overview of oral cancer risk factors

Oral cancer is a multifactorial disease. It has long been established that smoking or alcohol abuse plays a key role in the causation of oral cancer and acts synergistically (Ko *et al.*, 1995). Additionally, SLT is also declared by the IARC (2004) as an independent risk factor for mouth cancer. From ancient times, physicians were puzzled about the causes of cancer. God was blamed for causing cancer by the ancient Egyptians, and in the early days of medical science, humoral theory was used to explain the causes of cancer. According to the theory, four types of humor (body fluid) can be found in our body: blood, phlegm, yellow bile and black bile. An excess amount of black bile in any part of the body was believed to cause cancer (Ballantyne, 1988) and the theory was unchallenged for 1,300 years. Later, it was replaced by another theory, the lymph theory, which proclaimed another body fluid (lymph) was thought to cause cancer. In 1838, the German pathologist Johannes Müller replaced this theory with the blastema theory. Müller proposed that cancer is made up of cells, not body fluid, and cancer cells did not come from normal cells but rather from blastema. The blastema theory was later replaced by the chronic irritation theory, which suggested that chronic irritability causes cancer and spreads like a fluid in the body. This theory was later replaced by the infectious disease theory. Two doctors from Holland concluded that cancer is contagious and proposed that cancer patients should be isolated to prevent the spread of the disease (American Cancer Society, 2014).

During the early 19th century, monofactorial disease causation theory came into existence. Based on this theory, every disease has one cause that in limited circumstances is sufficient to cause a specific disease (Broadbent, 2009). However, it was never believed that any disease was literally monocausal and had a single cause, given no event is ever a product of single cause (Lee, 2012). However, according to Broadbent (2009), monocausal disease causation meant that a single cause that fulfils the criteria of Koch's postulates (in the 19th century Koch identified the microbial agents responsible for cholera, tuberculosis and anthrax) is regarded sufficient to establish the relationship between a specific microbe and the disease produced by that specific microbe. Although this model was fruitful in identifying potential microbial causal agents, it failed to explain the cause of increased incidence of chronic NCDs through a single causal factor (Broadbent, 2009). In response to this scenario, a multifactorial disease causation model was proposed in the mid-20th century.

Multifactorial disease causation model

The multifactorial disease causation model was developed due to the increased number of chronic NCDs (diabetes, heart disease and cancers) that could not be explained in reference to a single causal factor. The model was developed from the central metaphor of *web causation.* According to Krieger (1994):

> *Conceptually, the metaphor evoked the powerful image of a spider's web, an elegantly linked network of delicate strands, the multiple intersections representing specific risk factors or outcomes, and the strands symbolising diverse*

causal pathways. It encouraged epidemiologists to look for multiple causes and multiple effects, and to identify the many—as opposed to singular—routes by which disease could be prevented.

Based on the multifactorial approach, a disease has many causes that may be present without the disease or absent when the disease is present (Broadbent, 2009). The selection of a multifactorial disease causation model for the present study can be justified based upon the work of Furman (2017). According to Furman, a monocausal model of disease causation is useful to explain an infectious disease, which is typically a microbial disease, but its use is restricted to the biomedical sciences, such as virology, immunology, microbiology etc. In contrast, a multifactorial disease causation model is effective for explaining chronic NCDs and is more closely linked to epidemiology. For the present study, the aim was to examine the risk of developing oral cancer from SLT use. Oral cancer is a multifactorial chronic NCD for which a single detectable cause has not been found. Moreover, the role of any individual factor is poorly understood, including personal habits (smoking, SLT, alcohol use), several types of infections (viral, bacterial or fungal), other extrinsic factors (oral hygiene, radiation, industrial hazards) and intrinsic factors (genetic, nutritional deficiency, immunodeficiencies, BMI; Oji and Chukwuneke, 2012). Also, these risk factors often act synergistically; therefore, understanding the risk of developing oral cancer from SLT use would require a multifactorial approach rather than a monofactorial approach. This is supported by Peng *et al.,* (2016), who highlighted the importance of a multifactorial approach of aetiology analysis to improve the treatment of oral cancer.

For the present study, to understand the relationship between SLT use and oral cancer risk among Bangladeshi adults, detailed information concerning SLT use (type of SLT, duration of use, amount usage per day, age of onset) was recorded. While considering the multifactorial disease causation approach, the present study collected information related to other established risk factors, such as smoking (type of smoking—cigarettes, bidi, waterpipe, duration of usage, number of cig/bidi/waterpipe per day, age of initiation), alcoholism (type of alcohol, quantity, frequency, duration of usage and age of initiation). Additionally, other putative risk factors, such as oral health indicators (partial and complete dentures, teeth cleaning instruments, frequency of cleaning, substance used to clean teeth, status of gum bleeding, status of cuts or ulcers, frequency of dental visits), family history of cancer (relationship, age of diagnosis, type of cancer) and BMI were included. However, other possible risk factors, such as viral infection and diet, were excluded from the present study.

2.2.7 Overall summary

The overall findings of the review suggest a strong link between several forms of SLT use and oral cancer risk. However, controversy remained between the studies from the industrialised countries and developing countries. Most studies from SEAR, African and Eastern Mediterranean region supports the strong relationship between SLT use and oral cancer risk. However, studies from industrial countries reported mixed findings. Scandinavian studies did not observe an increased oral cancer risk among SLT users and studies from Europe and America reported minor or weak association between SLT use and oral cancer. The dose-response relationship was observed between SLT use and oral cancer incidence. with a higher frequency and longer duration of SLT use being associated with an increased risk of oral cancer. The risk of oral cancer varied substantially from different type of SLT use and its preparation. Both BQ with and without tobacco increased oral cancer risk. The risk was higher among BQ with tobacco users. Disparities remained regarding the increased oral cancer risk for BQ chewing without tobacco. Most studies from Asia pacific region found strong association between BQ without tobacco use and oral cancer risk. However, several studies from India reported non-significant or minimal association between chewing BQ without tobacco and oral cancer risk. Regrading other risk factors, smoking increases oral cancer risk substantially. Several studies found that traditionally manufactured smoked tobacco, also known as bidi, increased oral cancer risk substantially but did not find any association between oral cancer and cigarette smoking. The association between oral cancer and alcohol drinking was inconsistent and varied globally. The joint effect of smoking and SLT use and smoking, SLT use and alcohol drinking was higher than their individual effect. Among other putative factors, poor oral hygiene, lower BMI, dietary deficiency and HPV infection increased oral cancer risk.

Chapter III. Methodology

3.1 Introduction

The purpose of this PhD was to examine the factors contributing to adolescents SLT use in Bangladesh and investigate the role of SLT in oral carcinogenesis among Bangladeshi adults. Thus, the study findings will inform the appropriate interventions and policy to reduce the future and current burden of SLT-related harm in Bangladesh. The aim of this chapter is to exhibit the research methodology to attain the study objectives. The chapter is presented in three separate sections. The first section deals with the overall research methodology and the choice of suitable methods. The critical analysis of the strengths and limitations of the chosen methods and their alternatives are also discussed. The second section demonstrates the adolescent cross-sectional survey method, and it explores the study setting, target population, sampling frame, study measures, survey tool and its validity, the outcome of the pilot study, data analysis procedure and ethical issues. The last section of the chapter illustrates the hospital-based case-control study method and it explains the study setting, selection criteria for cases and controls, sources of cases and controls, justification of matched design, sample size and power calculation. In addition, last section of the chapter will demonstrate how quality was maintained while collecting data for the hospital-based case-control study, procedure of recruiting study participants, data collection tool, study measures, data management and analysis strategies and lastly ethical issues and how they were managed.

3.2 Research design

The present study followed an observational study design. Observational studies are a type of analytic study design and known as epidemiological study. They are categorised into two main groups: experimental studies and observational studies (see Figure 9). The differential characteristics between observational study and experimental study is that of the presence and absence of interventions (Song and Chung, 2010). As described by Streiner and Norman (2009), in experimental study design, intervention is under the control of the researcher. He or she may decide which subject is receiving novel treatment or traditional treatment (no-treatment). The aim of this approach is to determine how changes in the independent variable affect dependent or outcome variable.

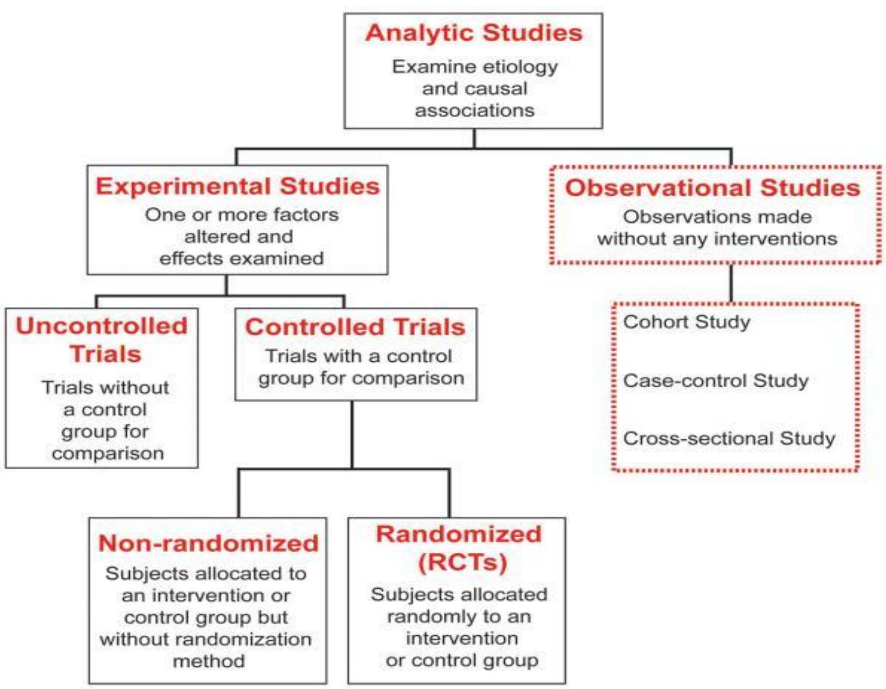


Figure 9: Analytic study design, (Source: Song and Chung,2010)

By contrast in observational study, the researcher does not intervene instead observe and evaluate the relationship between the exposure and the disease or dependent variable. There are three main types of observational study designs that are distinguished by the objective of the research study: Cross-sectional study, cohort study, and case-control study (Carlson and Morrison, 2009).

Cross-Sectional study

The cross-sectional study is a type of observational study where exposure and outcome are determined simultaneously for each participant. This design is the primary choice for prevalence study and requires a relatively shorter time and fewer resources to conduct (Carlson and Morrison, 2009). However, as the exposure and outcome are measured concurrently, therefore, there is no evidence of the historical relationship between the exposure and outcome. This means the researcher may determine the association between the exposure and outcome but there is generally no evidence that the exposer has caused the outcome.

Cohort study

The cohort study design is characterised by the fact that study subjects are followed over a period. The study design begins with individuals who are exposed and not exposed to a risk factor and then assesses the subsequent development of a specific disease (See Figure 10). This study design is ideal when the exposure is rare, but the outcome is common or relatively not rare (Carlson and Morrison, 2009).

Case-control study

Case-control study design begins with comparing individuals who have already developed the outcome of interest (cases) with an individual who does not have the outcome (Controls). The comparison is conducted according to a history of exposure to certain factors. The design is appropriate when the outcome of interest is rare (see Figure 11). However, a major limitation of the case-control study design is recall bias.

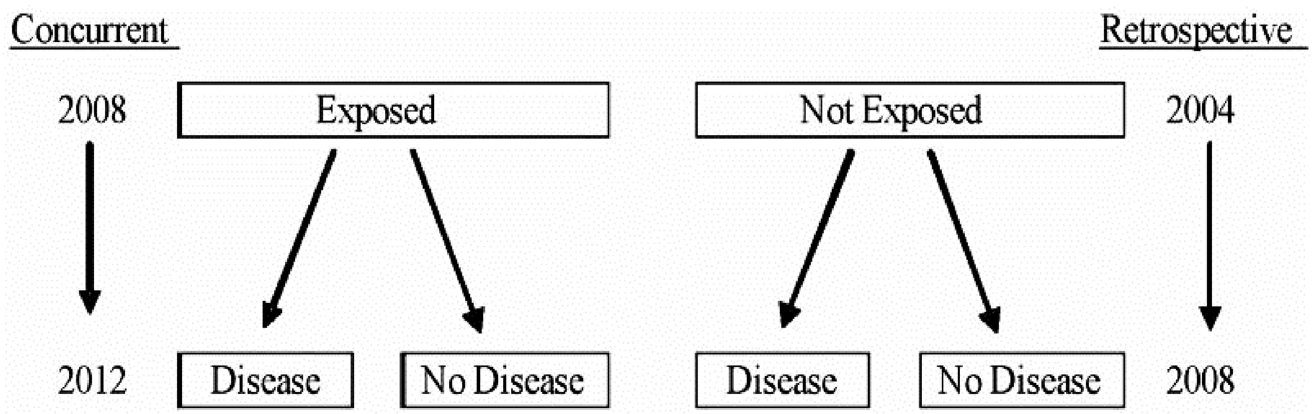


Figure 10: Cohort study Design

Considering the aim and objectives along with the applicability, the cross-sectional survey and the case-control study design were appropriate methods for the present study. One of the study goals was to look at the SLT use among Bangladeshi adolescents; using a cross-sectional method was an economical and realistic option to obtain a large amount of data within a limited time.

Another goal of the present study was to explore the association between SLT use and oral cancer risk among Bangladeshi subjects. Oral cancer is a relatively rare disease, and the exposure of interest (SLT use) is prevalent in Bangladesh.

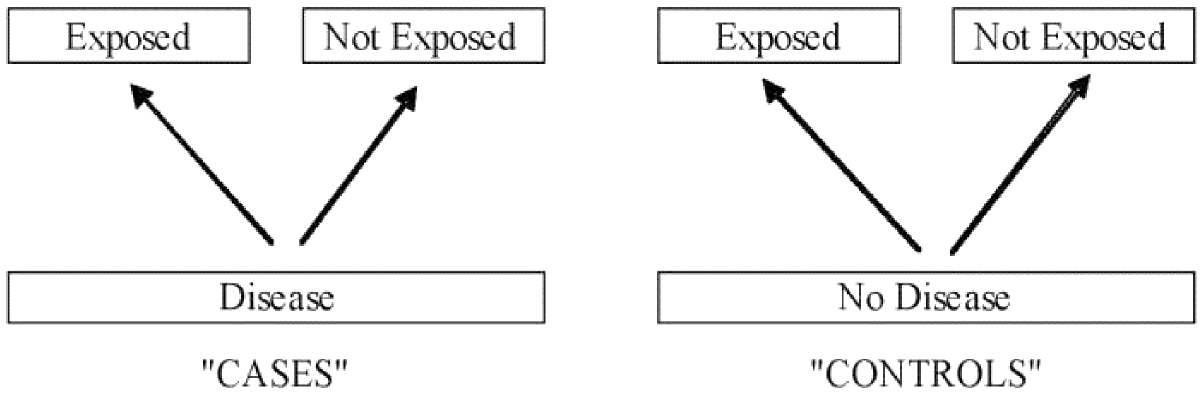


Figure 11: Case-control study design

Therefore, adopting the case-control study design was the only viable and cost-effective method. Table 16 Below compares different types of observational study and their applications.

Table 16: Different types of Observational study design

Type of observational study design	Subject selection	Sequence	Strengths	Weakness	Possible application
Cohort	Exposure status	Disease assessed following exposure	Generally, less measurement error; provides estimate of incidence; can examine multiple outcomes	May require larger samples sizes and long follow-up	Exposure is rare; multiple outcomes of interest; common outcome(s)
Case-control	Disease status	Exposure assessed prior to disease	Multiple exposures can be examined; smaller sample size needed	Can only examine a single disease of interest, greater potential for bias in measuring exposure	The disease is rare; single disease of interest; common exposure
Cross-sectional	Neither exposure nor disease	Both exposure and disease assessed at the same time point	Straightforward subject selection	Lack of information on exposure timing and disease onset	Quick execution

(Source: Edward, 2014).

3.3 Conceptual framework

Previous study results suggested that tobacco habits occur primarily at young age and the patterns of product preferences established among adult (Gupta and Ray, 2003). A recent study from the US looked at the average age of SLT onset among 2800 adults (1490 women and 1310 men). The study findings showed that the average of age of SLT onset was 13 years old (Patten *et al.,* 2018). Latest, GATS report showed that the mean age of SLT initiation age in India was 18 years old (WHO, 2018c). However, this picture is completely different in Bangladesh. Several studies from Bangladesh reported that the mean age of SLT initiation among Bangladeshi adults was 31 years old (Heck *et al.,* 2012; Mia *et al.,* 2017). Hence, to reduce the growing burden of SLT use among in Bangladesh, interventions should focus on adolescents by limiting future SLT initiation. Additionally, the relationship between SLT use and NCDs such as, oral cancer yet to be established. Given the diversity of SLT products and its contents, it is essential to establish local evidences (NCI and CDC, 2014). Therefore, PhD took this unique approach to examine the key factors of adolescents SLT use in Bangladesh as well as investigate the oral cancer risk from SLT use among Bangladeshi adults. Thus, the findings of the present study will inform the health promotion and intervention to reduce the future and current burden of SLT use in Bangladesh. Figure 12 below illustrate the conceptual framework of the present study.

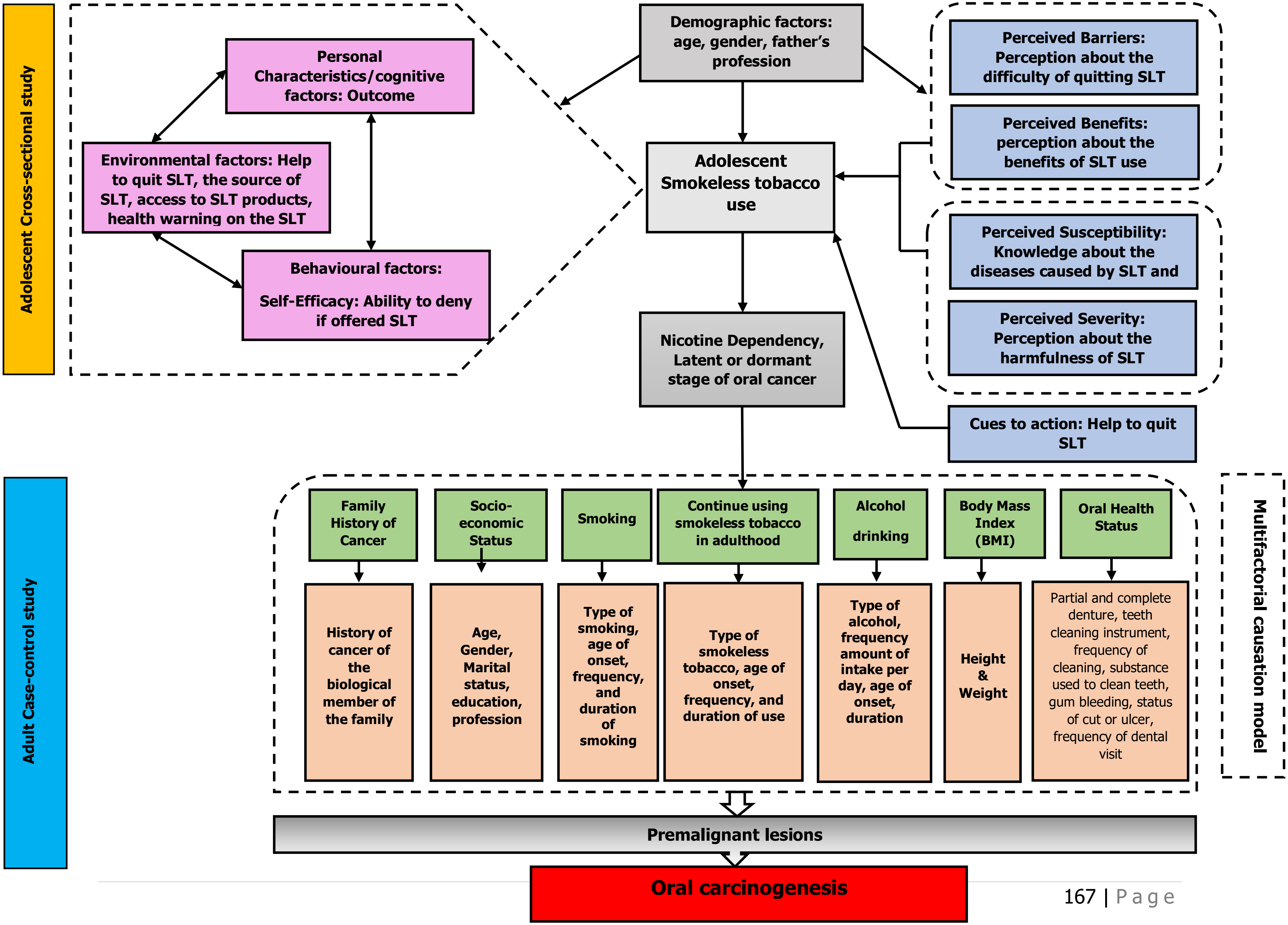


Figure 12: Conceptual framework

3.4 Adolescent cross-sectional survey method

The primary goal of the cross-sectional study was to survey students from grades 7-9 in rural secondary schools in Bangladesh. The survey objectives were to examine the vurrent practice and pattern of SLT use, determine the knowledge and perceptions about the use and harmful effects of SLT and, lastly to locate the predictors of current SLT use.

3.4.1 Study setting

This was a school-based cross-sectional study conducted in two rural non-government secondary schools located in Ramgati upazila, Lakshmipur district of Chittagong division in Bangladesh (see Figure 13). The Upazila covers 570 square kilometres and consists of 31 villages. There are total 55,664 households with a population of 26,61,002, of which males 1,24,449 and females 1,32,553. The density of population is 752 people per square kilometre. Of the total population, 94.80% are Muslim, 5.18% are Hindus, and 0.02% are of other religions. The average literacy rate of Ramgati is 39.3% (40.4% male and 38.3% female) compared to the national literacy rate of 61.5% (Bangladesh Bureau of Statistics, 2017). This area is predominantly a lower-middle class community. In this Upazila, agriculture is the primary source of employment (66.56%) followed by business 11.25%. There were total of 54 government primary schools (grade 1-5), 37 non-government primary schools, 18 non-government secondary schools, one government college and three non-government colleges in this upazilla. The total enrolment for the secondary schools was 8994. Among them 47.8% were male, and 52.1% were female students. However, there was no government secondary school in this area (Bangladesh Bureau of Statistics, 2017).

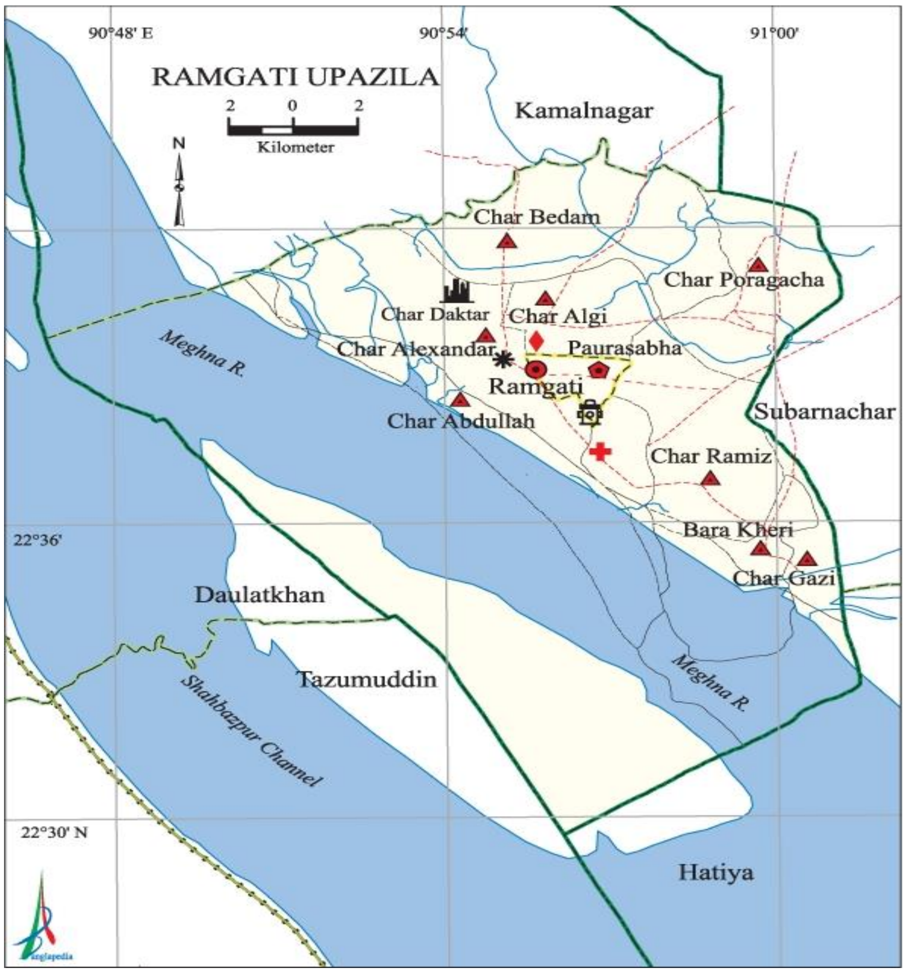


Figure 13: Ramgati Upazila

The current prevalence of SLT uses in Ramgati upazila, or Laxmipur was not available. However, the current prevalence of SLT use in Chittagong division was 19.5%. Male prevalence of SLT use in this division is 16.7% and female 21.9% (Sobhan, Choudhury, and Chowdhury, 2015). Given the scenario of socio-economic status of this community, it can be argued that the SLT use is highly prevalent in Ramgati Upazila. A previous Tobaco Control Survey also known as ITC study was conducted in 20 districts of 64 districts in Bangladesh reported that the SLT use is highly prevalent (33.2%) among the population from the low socio-economic background in rural areas of Bangladesh (Nargis *et al.,* 2015).

3.4.2 Target population

The target population for the current study was adolescents from rural areas of Bangladesh. There are nearly 29.5 million adolescents (10-19 years old) in Bangladesh among them 14.4 million are girls and 15.1 million are boys together represents nearly one-fifth of the country's total population of 157 million (Chowdhury, 2016). Secondary school enrolment of the country is still low at only seven million (38%). Moreover, the dropout rate of the secondary school is much higher than primary school, nearly 48% girls and 38% boy's dropout from the secondary school.

Different forms of tobacco use are widespread among adults in Bangladesh, more than 40% of the adult population uses varieties of tobacco products (WHO, 2009). The social acceptability, culture and poor implementation of tobacco control law is likely to encourage Bangladeshi adolescents to take up the habits of smoking and SLT use. A study among Bangladeshi adolescents showed 38.3% adolescents were able to buy tobacco products from the shop and more than 97% was not refused to purchase tobacco because of there age. Additionally, most adolescents exposed to tobacco advertisement (Islam, *et al.*, 2016). The availability and poor implementation of tobacco control are widely prevalent in rural areas compared to urban areas of Bangladesh (Nargis, *et al.*, 2015). Considering the above scenario, it can be argued that the adolescents from rural areas of Bangladesh are at higher risk of taking up SLT habits.

3.4.3 Sampling frame

There were 18 non-governmental secondary schools in Ramgati Upazila with no government secondary school. Total enrolment size for the grade 7 to 9 in 18 secondary schools were 8,994. Among them, 790 (8.78%) adolescents were recruited using stratified sampling method from two of the rural schools based on the enrolment size of the schools. Initially, five schools with the highest enrolment size were selected and from those five schools, two schools were chosen randomly from their registration number.

To reach a 95% confidence level, a sample size of 553 was required (Daniel, 2009).

$n = Z^2P\ (1-P)/d^2$

n = Desired Sample size.

z Statistics = for 95% Confidence Interval ‘Z’ value is 1.96.

p = Expected ever prevalence value was 10.1% = 0.10 (WHO, 2015).

d = Margin of error (with 2.5% precision value, d = 0.025).

3.4.4 Survey instrument

The data collection tool for the school survey was adapted from the Smokeless Tobacco module of the Global Youth Tobacco Survey (GYTS) questionnaire version 1.00 (2012) (Global Youth Tobacco Survey Collaborative Group, 2012) (see the Appendix B). There were additional questions on type of SLT use and eight knowledge questions were added from similarly selected literature and validated surveys (Kaduri *et al*., 2008; Abdullah *et al.,* 2014; Bhaskar *et al.,* 2016). The questionnaire had a total of 28 items that assessed the demographic information, SLT uses behaviour, perception and knowledge about the harmful effects of SLT. Students were asked to indicate responses to the questions by ticking the section that represents their answer. Confidentiality of answers was stressed by assuring students that not mentioning their name anywhere in the answer sheet and returning the questionnaire in a sealed envelope that was provided during the survey. The questionnaire was guided by Social Cognitive Theory (SCT) and the Health Belief Model (HBM) and comprised of closed-ended, open-ended and multiple response questions.

3.4.5 Validity and reliability of the survey instrument

3.4.5.1 Validity

Pilot study

As mentioned earlier the survey instrument in the present study was adapted and modified form existing GYTS questionnaire. The reliability and validity of the reasoning provided by the questionnaire of the present study was established through a pilot study. The pilot study helped to ensure the face validity of the questionnaire (Alumran, Hou and Hurst, 2012). That means, in respondents' opinion the questionnaire was able to measure what they are intended to measure. The pilot study helped to determine the suitability whether the format and content of the SLT use behaviours being measured, the level of difficulty and the length of time to complete the questionnaire. The content validity of the study was assessed by soliciting feedback from the teachers and local health care professionals as to the relevance of the questions, given the behaviour that was measured.

The questionnaire was piloted among five female and five male students from two secondary schools which did not participate in the main study. Additionally, students were asked to comment on the length, level of difficulty and whether the directions and language were clear. Also, whether the title and purpose of the school survey were clearly understood to determine validity and make improvement of the questionnaire for the main study. Students who participated in the pilot study also completed a questionnaire to improve the survey (see Appendix-L) Standard validation questions suggested by early study by Stacy (1987) were used to assess the validity of the inferences of the survey instrument for the present study.

Table 17: Pilot study result

Item name	Student feedback (n=10)
Title of the questionnaire is clear	97%
Direction of the questionnaire clear	94%
Clearly understood the question	90%
Appropriate language was used	89%
The length of the question is appropriate	94%
Question is not too personal	100%
Multiple choice questions are complete	89%

Table 17 shows students' feedback on the questionnaire, 94% could understand the direction of the questionnaire, over 90% students thought the title was clear and 90% students could understand the question and 89% students thought the appropriate language was used and understood the meaning of the question. More than 90% students thought the length of the questionnaire was appropriate and 89% students thought the multiple-choice question was appropriate.

Self-reported data

The validity of self-reported data is a critical component of study related to adolescent health risk behaviour. Brener, Billy and Grady, (2003) examined over 100 studies related to adolescent tobacco, alcohol and other substance misuse. They identified two major factors while assessing the validity of self-reported data. They are: cognitive issues and situational issues. Cognitive issues address whether the respondents understand the question and have appropriate knowledge or memory to answer the question. Therefore, the survey questions were designed meticulously to make sure respondents understood the terms used in the question. They also tested the participants' ability to recall information.

Situational issues refer to the influence of the setting of the survey-e.g., at school or at home- on the responses. The context can influence survey responses- e.g., adolescents may be reluctant to admit that they got drunk if they think their parents will have access to the response or exaggerate the response if they think their peer will see their response. Therefore, the setting where the survey is administrated is important. However, the best result can be achieved when a strong sense of anonymity and little fear of judgement can be ensured.

To address the cognitive issue, the questionnaire was translated from English to Bengali and then backtranslated to English by professional translators. As mentioned earlier the questionnaire was reviewed by the research team and local healthcare workers who had previously conducted surveys in schools to ensure that the Bengali version was idiomatically appropriate for Bangladeshi adolescents. To ensure accurate recall of the SLT use behaviour, respondents were asked about their SLT use behaviour in the last 30 days.

The situational issues (related to the validity of self-reported data in the present study) were mitigated by the socio-cultural factors related to SLT use in Bangladesh. In Bangladesh SLT use is regarded as a shared social activity – performed with relatives, friends, and family – rather than a detrimental behaviour. It is integrated into social gatherings – such as festival, wedding, religious gathering (Sansone, 2014). In Bangladeshi society younger people hesitate to smoke before their elders and they will never smoke cigarettes in front of their parents or seniors. However, SLT is an exception. Chewing pan or betel leaf along tobacco products regarded as normal social behaviour and considered as a symbol of hospitality in the rural areas of Bangladesh. Given the socio-cultural scenario, adolescents were more likely to give an honest answer. Additionally, a strong sense of anonymity was ensured by not writing the participants name in the questionnaire and returning the answer in a sealed envelope.

3.4.5.2 Reliability

Cronbach's alpha is a standard measure of internal consistency and one of the methods of measuring reliability and it is used to determine how much the items on a scale measure the same underlying dimension (Connelly, 2011). The questions on the SLT habit section were adapted from the Global youth tobacco survey Questionnaire's

Smokeless tobacco module. The internal consistency (Cronbach's alpha) of the subscale items of the GYTS questionnaire was reported ranged from 0.70 to 0.94 indicating the good internal consistency of the survey instrument (Chen, Chiou and Chen, 2008). The internal consistency of the knowledge items was also calculated by using Cronbach alpha technique. The knowledge scale consisted of eight items. The scale had a prominent level of internal consistency, as determined by a Cronbach's alpha of 0.79. However, no test-retest reliability of the questionnaire was conducted due to limited resources and time.

3.4.6 Data collection procedures

The school survey did not require school board of members approval. However, both verbal and written consent was obtained from the school head teacher (see Appendix C). Both schools and students were free to decide whether they wanted to participate in the study. School authority was responsible for distributing a standardised introductory letter to the parents which was submitted to the head teacher of the school and each child took the letter to their parents. Approval for participation in the survey was based on passive consent from the parents and they had seven days to withdraw their child from the survey (see Appendix D). The approval rate was 100% — none of the parents withdrawn their child from the survey. Regardless of the SLT use status, all the students presented in the class were eligible to participate in the study. Students were asked to complete the survey questionnaire after explaining the purpose of the study and the instructions to fill in the questionnaire. School authority was requested not to be present in the class during completing the questionnaire to ensure respondent felt free to give the honest answers. Participants were assured of confidentiality of the information provided and encouraged to be honest with their answers. A student representative was selected to collect the completed questionnaires in a sealed envelope from the students. The survey was administrated during a single class period and took approximately 15 minutes to complete. At the end of the survey, the researcher also provided a free oral hygiene instruction session for the students.

3.4.7 Measures

3.4.7.1 Dependent measures

The dependent measure or outcome variable for the present study was SLT use. This variable was subdivided in three main categories: *ever* SLT user, *current* SLT users and never users. For this study "ever" SLT users were defined as respondents who had tried SLT at least once in their lifetime (even a tiny portion). "Current" SLT users were defined as respondents who had tried SLT at least once in last 30 days prior to the survey and 'never users' had never tried SL before (WHO, 2015). Additionally, respondents were asked about the type of SLT they have tried.

3.4.7.2 Independent measures

Socio-demographic measures

Socio-demographic characteristics were measured in three items, included age and gender of the respondents and the parental occupations.

Smokeless tobacco use behaviour measures

SLT initiation age was recorded along with the frequency of SLT use. SLT dependency was measured using four items. Students were asked how many times they have used SLT in past 30 days, frequency of use per day, desire to have SLT first thing in the morning and their desire to use it again just after using SLT. To understand the outcome expectancies respondents were asked the reasons for using SLT. SLT cessation behaviour was measured with five items. Students were asked about their intention to quit SLT, the status of the success of quitting attempt, the status of receiving help to quit SLT, and their perception about the difficulty of quitting SLT.

Access and availability

To measure the availability of SLT products, students were asked about the source of SLT in last 30 days. The answers included both social sources (got it from someone), and commercial sources (school canteen, the street vendor, stores near the house or school)

To measure the accessibility of SLT products, students were asked if they were refused to buy SLT because of their age. Respondents exposure to health warning on SLT packages and their perception about the anti-tobacco message was measured asking if they have seen any health warning on SLT packages during last 30 days and if that led them to think to quit SLT.

Self-efficacy

To understand the peer pressure and ability to refuse SLT, respondents were asked about their perception of using SLT if offered by a friend. Responses were recorded in 4-point Likert scale (definitely not, probably not, probably yes and definitely yes).

Knowledge about the harmful effects of SLT use

To assess respondent's knowledge about the harmful effect of SLT use and its content, eight questions were asked. Primarily it was regarded as a categorical variable. Later, a new variable was created based on the knowledge score. The knowledge score was ranged from 0 to 8, where 'one' score was allocated for each correct answer. The knowledge score was further categorised into: poor knowledge (score of 0-2), average knowledge (score of 3-5), and good knowledge (score of 6-8) for the predictive model knowledge score was considered as a categorical variable (see Appendix E).

3.4.8 Data analysis procedure

All the analyses were conducted using SPSS version 24. Data analyses conducted in multiple phases. In the first phase, simple descriptive analysis (frequency, percentage, mean, median etc.) was conducted to examine the current SLT use behaviour, perception and knowledge about its ill effect. In the second phase, statistical analyses were performed to explore the association between different variables such as socio-demographic variables, SLT use behaviours, perception and knowledge. Association between categorical variables were assessed using Chi-Square or Fisher-exact test when appropriate. Knowledge was assessed using a scoring system where participants were given one point for each correctly answered question and zero otherwise. The Sum of scores was calculated, and its relation to other variables was assessed using Student t-test or Mann-Whitney test when appropriate. Additionally, Chi-Square or Fisher-exact test was used to assess the association between knowledge categories (Poor knowledge, Average knowledge, and good knowledge) and other variables.

In the third phase, univariate and multivariate binominal logistic regression analysis was performed to locate the predictors of current SLT use. Binominal logistic regression is part of Generalised Liner Model and extension of liner model which integrate the dependent variables which are not continuous. It allows for a relationship to be modelled between several independent variables and a single dependent variable where the dependent variable is dichotomous. Additionally, instead of predicting the category of the binomial logistic regression directly, the logit of the dependent variable is predicted instead. Therefore, if five independent variables are represented through "X1" to "X5" and the dependent variable to be "y", then the binomial logistic regression model would be:

$$\boldsymbol{logit(Y) = \beta 0 + \beta 1X1 + \beta 2X2 + \beta 3X3 + \beta 4X4 + \beta 4X5 + \varepsilon.}$$

Here, β○ is the constant, β_1 is the slope coefficient for X_1 and so on, and ε is the errors. Therefore, it can be estimated as below:

$$\boldsymbol{log\,it}(\boldsymbol{Y}) = \boldsymbol{b_0} + \boldsymbol{b_1 X_1} + \boldsymbol{b_2 X_2} + \boldsymbol{b_3 X_3} + \boldsymbol{b_4 X_4} + \boldsymbol{b_5 X_5} + \boldsymbol{e}$$

Here, b_0 is the constant that estimates the β_0, b_1 is the sample slope parameter for $x_1$and so on, e represents the errors and estimates ε and *logit* is the log of the odds of an event occurring.

Below steps were followed to build a logistic regression model to locate the predictors of current SLT use:

First, univariate logistic regression was conducted to locate the unadjusted association between the dependent and independent variables. Akaike information criterion (AIC) was also extracted for each variable. Some variables were present with different cut-off values. Each of these them was assessed and the variable with the lowest AIC was included in the final model. A *P*-value of smaller than 0.25 was included in the multivariate analysis and the cut-off value of 0.25 was also supported by the previous research (Mickey and Greenland, 1989). Some of the variable such as gender was included in the multivariate analysis although turned-out insignificant in the univariate analysis. As the previous study showed gender is a significant predictor of adolescent's SLT use (Agaku*, et al*., 2014)

Secondly, variables that were significant in the initial screening (univariate logistic regression) were included in the multivariate logistic regression. Correlation matrix was also constructed to ensure the absence of multicollinearity between variables included in the model. Exponentiated coefficients (odds ratio) were extracted from the model as well as the overall AIC of the model. 95% confidence intervals and Wald statistic were used to assess whether regression coefficients were significantly different from zero (null hypothesis). Receiver operator characteristics curve was plotted to assess whether the model can accurately classify the data through AUC (Area under curve). An AUC of 0.8 or higher was a good indicator of the model predictive power. The goodness of fit measures such as McFadden and Nagelkerke R2 were also assessed. Deviance residuals were plotted to assess outliers - as well as influence and leverage points - in the data. The accuracy of the model was also assessed by calculating the percentage of accurate predictions made by the model (Accuracy= [True positive + True negative] * 100 /Total number of observations. Likelihood ratio was also calculated to assess whether the model was significantly different from the null model (see Appendix F for the model diagnostics).

3.4.9 Ethical issues

Ethical approval for the present study was obtained from the Anglia Ruskin University Ethics committee (see Appendix I) and the head teachers of the participating schools in Ramgati Upazila. Informed consent was obtained from the students' parents (see Appendix-D). Prior to the administration of the survey, the researcher (MZU) explained the purpose of the study and the students were required to provide verbal consent to indicate voluntary participation. Students were informed of their right to decline participation or withdraw from the study at any time without any consequences. The confidentiality and anonymity of the study participants were ensured by not including their name in the survey and returning the completed questionnaire in a sealed envelop.

3.5 Hospital-based case-control study

3.5.1 Design overview

The hospital-based case-control study design was adopted to explore the relationship between SLT use and oral cancer incidence in Bangladesh. The case-control is a type of observational study in which subjects with a specific disease (cases) of interest are compared with subjects who do not have the disease (control) (see Figure 15). Specific information is collected from both groups concerning their previous exposure to investigate the relationships between exposure and the disease of interest (Peat and Williams, 2002). Woodward (2013, p.243) offered common advantages and disadvantages of case-control studies:

Advantages

I. Less time intensive and inexpensive compared with other observational designs. The case-control design is most suitable for diseases with a longer latency as there is no waiting time involved.

II. Multiple risk factors can be examined simultaneously. For example, asking a series of lifestyle questions can help to identify several risk factors concurrently.

III. It is particularly suited for an investigation of risk factors of rare diseases.

IV. Generally, it requires a smaller sample size in comparison with a cohort study. As case-control study's sample size depend upon the prevalence of exposure rather than rate of outcome.

V. For the same overall sample size, it is possible to evaluate confounding interactions more precisely compared with a cohort study because subsamples are equally balanced in case-control studies.

VI. Better quality of exposure data by interviewing study participants which is often impossible in much larger cohort studies that have to rely on self-administered questionnaires.

Disadvantages

- In a case-control study exposure is not assessed prior to, but simultaneously with the disease. So, no time sequence can be established; therefore, the results cannot be used to demonstrate causality. Additionally, frequent problems have been noted with the accuracy of recall (recall bias).
- A case-control study can investigate only one disease outcome at a time.
- This design cannot provide a valid estimate of risks or odds. It can only provide an approximation of relative risk, which may be inaccurate in certain circumstances.

- The most common criticism is that different types of bias may operate, in particular selection bias in cases and/or controls and reversed causation meaning that the presence of disease in cases influences the assessment of exposure.

3.5.2 Justification of design selection

Case-control is a standard design choice when investigating health outcomes that are relatively rare and characterised by a long latency period (Bruce, Pope, and Stanistreet, 2018). For diseases that are sufficiently rare, choosing a cohort study design becomes impractical because it would take too long before an adequate number of cohort members contract the rare disease of interest. Given the fact that oral cancer is an uncommon chronic disease with a long preclinical stage (Ghantous, Yaffi and Abu-Elnaaj, 2015), a cohort study would be too time-consuming and too costly to investigate the relationship between SLT use and oral cancer. Moreover, if the rate of exposure is also rare, one must use a special cohort study, and if both outcome and exposure are rare, a two-stage design will be the only option as it allows oversampling of both exposed and diseased subjects (Rothman, Greenland and Lash, 2012). Due to a lack of accurate records of past exposure in Bangladesh, a retrospective cohort study would be impossible to employ in this scenario, making the case-control design the best alternative.

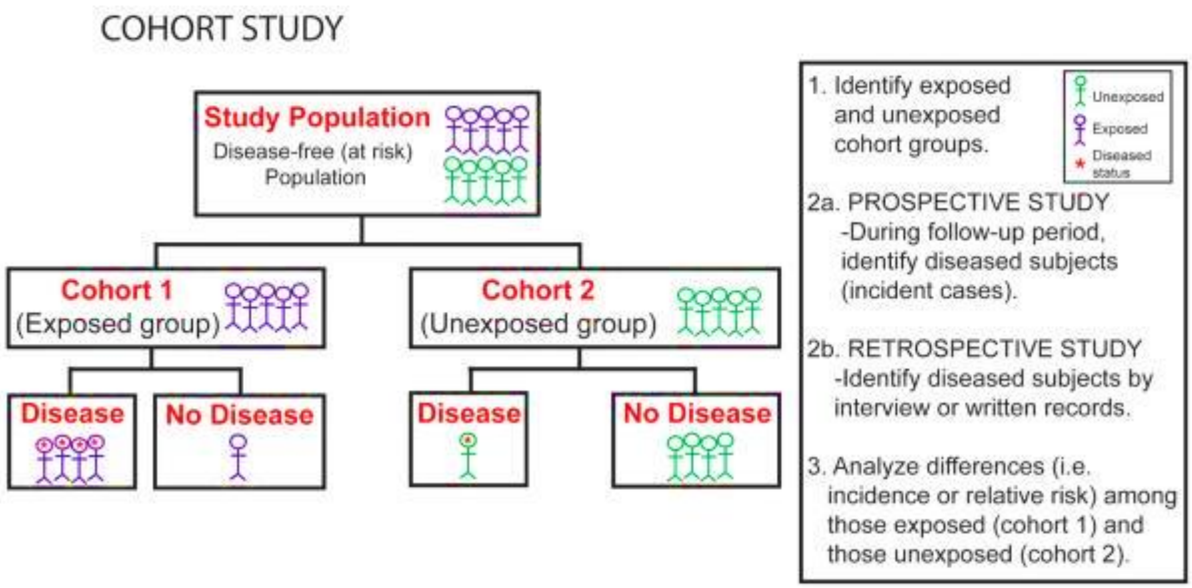


Figure 14: Cohort study

Case-control studies are used for the pragmatic reasons of both cost and time savings rather than for considerations of validity. According to Rothman, Greenland, and Lash, (2012) case-control studies have suffered from a reputation of poor conduct and over interpretation of the results as an inherent weakness of the design. Although a cohort study is more appropriate for life course epidemiology of chronic diseases, one caution is that it is costlier and more time-consuming (Gerstman, 2013). Because in a cohort study, the exposure of interest is measured in the present time and cohort participants are subsequently followed up over time in order to determine the occurrence of disease (see Figure 14).

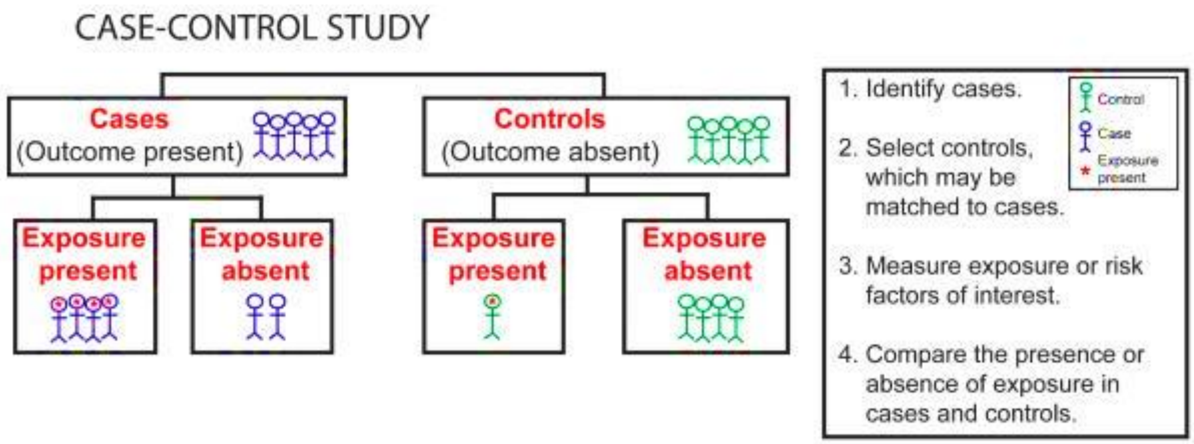


Figure 15: Case-control study

3.5.3 Research setting and study population

Oral cancer cases and controls were recruited from a government dental college hospital located in Dhaka City, Bangladesh between July 2015 and December 2015. The location and the description of study subjects are described below.

3.5.3.1 Study setting

The hospital, established in 1961, is the largest tertiary-level dental hospital in Bangladesh with 250 beds. The hospital currently serves more than 20 million citizens from Dhaka and its neighbouring cities (see Figure 16). The Oral and Maxillofacial Surgery department of the hospital manages all oral oncological patients. Patients from other neighbouring states are also referred to this hospital, since it is the only tertiary-level publicly funded dental hospital in Bangladesh. Since this hospital is the primary referral location for oral oncological patients from all over the country, it was the most appropriate location to recruit newly diagnosed oral cancer cases for the case-control study.

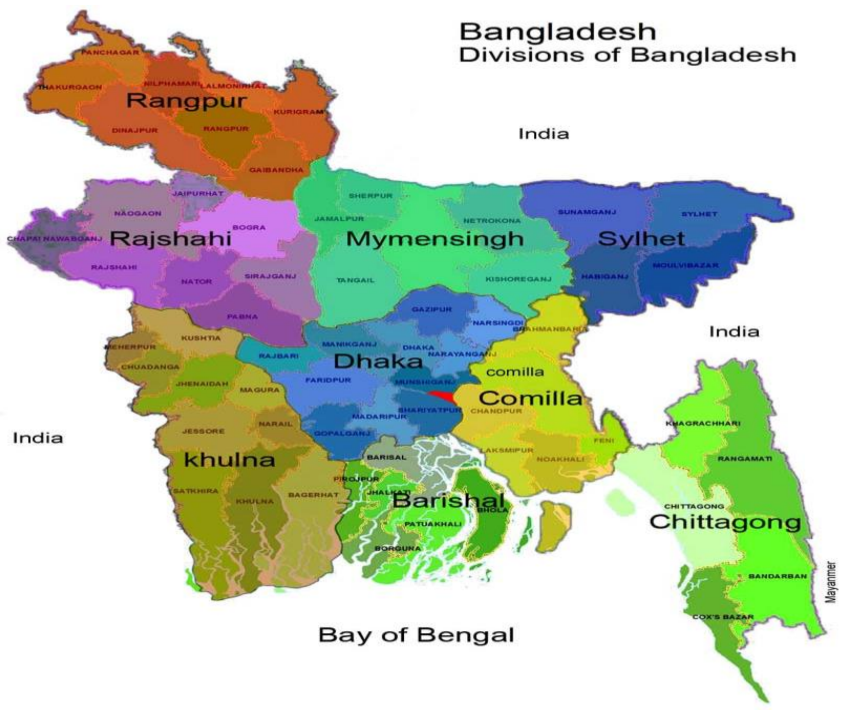


Figure 16: Map of Bangladesh

3.5.3.2 General selection criteria

To be eligible for the study, the subject must be Bangladeshi born with no previous history of cancer. Subjects who were severely ill or unable to provide reliable information were excluded from the study (see Section 3.5.3.7 and 3.5.3.9 for a complete list of inclusion/exclusion criteria).

3.5.3.3 Case selection

A total of 169 histologically and clinically confirmed new oral cancer cases were recruited for the study. A histologically confirmed diagnosis is regarded as the gold standard for most cancer cases, as recruiting less documented cases can raise validity issues (Silva, 1999). Additionally, accepting less documented cases creates the risk of diluting the case group with non-cases and reduces the chances of estimating the difference of exposure among cases and controls. Cases were selected based on the WHO's ICD-10 oral cancer classifications (WHO, 2016), which are described in Table 18 below.

Table 18: WHO's ICD-10: Oral cancer classification.

Type name	Cancer Site
C00.3	Upper lip, inner aspect
C00.4	Lower lip, inner aspect
C00.5	Lip, unspecified inner aspect,
C01 – C02	Base of the Tongue and other parts of the tongue
C03	Cancer of the Gum
C04	Floor of the mouth
C05	Hard palate and Soft palate
C06	Cheek mucosa, Vestibule of mouth, Retromolar area
C09	Tonsil

All the patients were recruited immediately after histopathological diagnosis between July 2015 and December 2015. Only incident cases (all new cases that were diagnosed during these six months) were recruited for the following reasons:

- The recall of exposure is likely to be more accurate among newly diagnosed cases. In addition, recently diagnosed patients are less likely to have changed their pre-diagnostic habits.
- Prevalent cases (all new and old cases that are present among the population at a particular time) may create recall bias and are less likely to be accurate about past exposure.

- In relation to survival and exposure, prevalent oral cancer cases are biased in terms of survival and the frequencies of exposure will differ between prevalent and incident cases (Schlesselman and Stolley, 1982).

3.5.3.4 Sources of cases

For the present case-control study, all the cases were recruited from a hospital setting. There are two main options for sourcing cases: hospital-based and population-based (Silva, 1999). The hospital-based case-control study has been criticised for its lack of generalisability of the study findings. Specifically, if cases are selected from a hospital, the identified risk factor may be unique for that particular hospital. However, as mentioned by the IARC, in a case-control study, validity of the study design is much more critical than the generalisability of the results (Silva, 1999). Nevertheless, selecting cases that are representative of the target population can strengthen the external validity of the study.

Concerning population-based cases, many communities maintain registries of patients and diseases, making these a reliable sampling source for a population-based case-control study (Song and Chung, 2010). Although the method sounds convenient, it may raise the issue of validity. For example, if cases were recruited from one specific hospital, recognised risk factors may be exclusive to that hospital. Moreover, the value of this source might be limited as there could be a substantial time lag between diagnosis and registration. Further, some patients may be deceased, and some may have moved out of the target area. Therefore, by the time the case is registered, it may not be possible to regard them as incident cases anymore.

Unlike other countries, no cancer registry is maintained at the community facilities in Bangladesh. Therefore, conducting a population-based case-control study is not possible. In addition, the hospital is the primary referral point for oral oncology patients. Due to the limited time and available resources, the hospital was the only feasible source.

3.5.3.5 Selection criteria of cases

Inclusion criteria for cases

- Newly diagnosed oral cancer cases who visited the primary referral hospital during July 2015 to December 2015.
- Patients who were diagnosed within a week after visiting the hospital visit.
- Patients who were not yet enrolled in any treatment procedure.
- Patients who were over 18 years of age.
- Patients who were fit (physically and mentally) to provide sufficiently reliable information.
- Patients who had signed the consent form.

- Patients who were diagnosed in a different hospital, but their primary treatment centre was the study hospital, and the diagnostic procedure in the previous hospital was conducted within the last week.

Exclusion criteria for cases:

- Patients who did not provide consent.
- Patients with recurrent oral cancer.
- Patients with pre-cancerous lesions.
- A patient who had already gone through the treatment procedure.
- Patients who presented with cognitive impairments.

3.5.3.6 Selection of controls

In a case-control study, selection of controls is crucial to ensure the internal validity of the study (Wacholder *et al.,* 1992). The primary function of controls is to provide information on the distribution of exposure within the population at risk of becoming a case (Rothman, Greenland, and Lash, 2012).

As suggested by Woodward (2014), there are several principles for selecting controls for a case-control study:

- Controls should be selected from the same study population. If this rule cannot be followed, there should be solid evidence that the population supplying controls has the same exposure as the population that is the source of cases.
- Within the strata of factors that will be used for stratification in the analysis, controls should be selected independently of their exposure status (i.e. random sampling within strata), so that the sampling rate for controls should not vary with exposure status (Rothman *et al.*, 2012).
- Controls should be free of the disease being studied. Moreover, controls should not qualify if they are disease-free, but had a history of the disease of interest in the past.

3.5.3.7 Sources of controls

Controls can be selected from several sources: hospital controls, population or community controls, and friends or relative controls (Rothman, Greenland, and Lash 2012). Controls for this study were selected from the outpatient department of the same hospital where cases were recruited. However, it is always hard to define the population residing in the very large catchment area where the cases arose. Selecting controls from the same catchment area as the cases will be difficult if not impossible, because the selected hospital is the tertiary and only dental hospital in Bangladesh. Therefore, using controls from the same hospital will lead to a less biased estimate of effect compared with community- or population-based controls (Rothman, Greenland, and Lash, 2012).

There is continuous debate on the advantage of hospital controls over population-based controls or vice versa. A study on cancer in a Chinese hospital conducted three parallel case-control studies on the risk factors for leukaemia, breast cancer, and colorectal cancer using both hospital- and population-based controls. When comparing both types of controls, the study concluded that hospital outpatients provide satisfactory control groups for a hospital-based case-control study (Li, Zhang, and Holman, 2013). However, a case-control study conducted among a group of hospitals in Canada suggested population-based controls are the best fit for hospital-based case-control study (Neupane, *et al.,* 2010). Though, they investigated acute cases (pneumonia) and restricted the study population to the hospital catchment area, which serves 1-2 million people. Nevertheless, limiting the catchment area for rare cases such as oral cancer would be a time-consuming and expensive process.

Recently a hospital-based case-control study was conducted in two cardiac hospitals in Bangladesh to explore the relationship between SLT use and risk of chronic heart disease. The study also compared the efficacy of hospital and community controls. Study findings showed there was no difference between hospital and community controls in terms of socio-demographics or risk variables and the observed association between disease and the risk factors were also similar (Rahman *et al.,* 2011). The study concluded that for a future case-control study conducted in a context of limited resources and a difficult socio-political environment, hospital controls could be enrolled in the hospital-based case-control study. Therefore, considering the above scenario, selecting hospital controls was the preferred approach for the present study.

3.5.3.8 Number of controls

Case-control studies usually include one to four controls per case to boost the statistical power of the analysis. Considering more than one control per case is justifiable for a hospital-based case-control study. However, increasing the control number to over four controls per case adds little or no statistical power (Hennessy *et al.,* 1999). Using multiple control groups involves considerable labour and cost. Additional controls should be included if it results in negligible cost and if controls are readily available.

Controls were recruited from the outpatient department of the hospital. For each case, two frequency matched (gender and age) controls were recruited. As mentioned earlier, it is always hard to define the source population when the hospital is the only tertiary-level dental hospital of a country. However, patients are referred to the hospital from various parts of the country for various dental-related problems. Therefore, recruiting controls from the hospital was the only logical option. To reduce the risk of underrepresenting the source population, in the current study we selected two controls per case (Rothman, Greenland, and Lash, 2012).

3.5.3.9 Selection criteria for controls

Inclusion criteria for controls

- Patients who visited the outpatient deprtment of the dental hospital during July 2015 to December 2015.
- Patients whose condition was not diagnosed more than one week earlier.
- Patients who were over 18 years of age.
- Patients who were fit (physically and mentally) to provide reliable information.
- Patient gender-matched with cases.
- Patient age matched with cases (+/- five years).
- Patient did not have a history of oral cancer.
- Patient did not have a history of pre-cancerous lesions.
- Agreed and signed consent form to participate in the study.

Exclusion criteria for controls

- Patients who are in the hospital due to tobacco or alcohol-related diseases.
- Physically and mentally debilitated patients who are unable to provide reliable information.
- A patient who had already gone through the treatment procedure.
- Patients who did not provide consent to take part in the study.

3.5.4 Justification of the matched design

Matching refers to the selection of a reference series—controls in a case-control study—that is identical, or nearly so, to the index series with respect to the distribution of one or more potential confounding factors (Rothman, Greenland, and Lash, 2012). Most commonly used matching variables are age and gender. In some circumstances, race, marital status, area of residence hospital etc. may be sensible matching criteria. Woodward (2014) provided a summary of the advantages and disadvantages of matching:

Advantages

- It allows for direct control of the potential confounding by matching variables. Meaning, the adjustment of the relationship between the risk factor and disease for the matching factors is achieved intuitively and leads to a clear interpretation in the sense that the observed associations are independent from the matching factors.
- It ensures that adjustment is possible.
- In some cases, matching improves the efficiency of the investigation, such as a smaller sample size could be used or the effect of a risk factor could be estimated within a smaller confidence interval.

Disadvantages

- Data collection procedures are more complex, as it may be difficult to find a suitable match for every case.
- Data analysis must account for the matching and requires matched analysis. The process is both complex to understand and compute.
- The effect of matching variables cannot be estimated.
- The effect of the risk factors cannot be estimated without adjusting the matching variable.
- If the matching is performed incorrectly, there is a chance of overmatching.

There are two types of matching in a case-control study: individual and frequency matched. Matching can be performed subject-by-subject, also known as individual matching, or for a group, also known as frequency matching.

For the present study, controls were frequency matched with cases based on age group and gender. It might be argued that matching in the case-control study might increase the efficiency of the stratified analysis rather than preventing confounders to distort the associations observed. However, if the matching variables were true confounders (and age and gender often are true confounders), the matched analysis would be more efficient (Woodward, 2014). Previous study results suggest that age and gender are associated with both SLT use and oral cancer (Sreeramareddy *et al*., 2014; Khan, Tönnies, and Müller, 2014). Therefore, age and gender were indentified as potential confounders in assessing the association between SLT and oral cancer. To control for the effect of these potential confounders, pair matching based on these characteristics was implemented and taken care of (adjusting in multivariate analysis) during the statistical analysis.

3.5.5 Estimated sample size

The estimated sample size for cases and controls were calculated to satisfy the power of 90% with a two-sided confidence interval of 95%. The sample size was based on a case to control ratio of 1:2. Estimated prevalence of exposure among controls was 25% (Nargis *et al.*, 2015) and among cases were set to 40%. The Fleiss method was used to calculate the sample size (Fleiss, Levin, and Paik, 2003). The estimated sample size for the cases was 157 and 314 for controls with a case to control ratio of 1:2 as per the calculation below:

$$n = (\frac{r+1}{r})\frac{(\overline{p})(1-\overline{p})(Z_{\beta}+Z_{\alpha/2})^2}{(p_1-p_2)^2}$$

n = sample size in the case group

r = ratio of controls to cases of 1:2

P = average proportion exposed = proportion of exposed cases + proportion of exposed controls / 2

Z β = standard normal variate for power = for 80% power it is 0.84, and for 90% power, the value is 1.28

Zα/2 = standard normal variate for level of confidence (at 5% type I error (*p < 0.05)* it is 1.96, and 1% type I error (*p < 0.01)* is 2.58)

p 1 – p 2 = effect size or difference in proportions exposed expected based on previous study, here p1 refers to the proportion among cases and p2 the proportion among controls

$$p_{case\exp} = \frac{ORp_{controls\exp}}{p_{controls\exp}(OR-1)+1}$$

P case exp = $\frac{2(0.25)}{0.25(2-1)+1} = \frac{0.50}{1 \cdot 25} = 0 \cdot 40$

Therefore, the average proportion of exposed would be, $\bar{p} = \frac{(0 \cdot 40 + 0 \cdot 25)}{2} = 0 \cdot 325$

The estimated sample size is calculated as follows:

$$n = (\frac{r+1}{r}) \frac{(\bar{p})(1-\bar{p})(Z_{\beta} + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

$$n = \left(\frac{2+1}{2}\right) \frac{(0.325)\ (1 - 0 \cdot 325)(1 \cdot 28 + 1 \cdot 96)^2}{(0 \cdot 40 - 0.25)^2}$$

$$n = (1.5) \times \frac{(0.325)\ (0.675)(10.49)}{0.022}$$

$$n = (1.5) \times \frac{(0.325)\ (0.675)(10.49)}{0.022}$$

$$n = (1.5) \times \frac{2.30}{0.022}$$

$$n = 1.5 \times 104.60$$

$$n = 157$$

Therefore, N = 471 (with a case-control ratio of 1:2, cases = 157 and controls = 314).

We successfully recruited 169 new oral cancer cases and 338 frequency matched controls maintaining a case to control ratio of 1:2. (See the Appendix K for post-hoc power calculation)

3.5.6 Quality assurance and quality control

Quality control and quality assurance are two significant contributors to the reliability of a case-control study (Blomgren *et al.,* 2006). Quality assurance refers to the activities that ensure the quality of the data before data collection, and quality control refers to the effort to monitor and maintain the quality of the data throughout the duration of the study (Szklo and Nieto, 2014). A systematic review conducted by Whitney, Lind, and Wahl (1998) regarding the importance of the quality assurance and quality control found that these are the most important practices of any study, as the conclusions drawn from the study are largely determined by the quality of the data collected. In particular, poor quality can decrease the power of the study and cause type II errors. Moreover, potential bias due to faulty instruments or errors concerning the implementation of study protocol may result in an incorrect report of relationships between the exposure variables and the disease (outcome) of interest (type I errors = false positives = failing to reject a true null hypothesis) or missing a true underlying association (type II errors = false negatives = failing to reject a false null hypothesis).

Therefore, minimising all potential errors is of paramount importance in the planning and implementation of the case-control study.

Traditionally quality assurance is comprised of detailed protocol preparation, data collection instrument development, procedures and manual of data collection procedures, and training and certification of staff. These activities are followed by a pre-test or pilot study with adjustments made as needed. In constrast, quality control activities include observations of procedures performed by the staff to identify any deviation from the study protocol and to ensure the validity and reliability of the study. Detailed quality assurance and quality control strategies for the current study are discussed below.

3.5.6.1 Quality assurance

Detailed study protocol

The study protocol contained a detailed description of the general components of the investigation. It described the general design and procedures used for the study and assisted staff members to understand the study context and specific activities to be performed. A detailed description of how the data collection activity should be conducted to maximise the likelihood of uniformity of the data collection procedures was also provided. For example, the research assistant was able to refer to the protocol to ensure familiarity with the inclusion and exclusion criteria for the cases (histopathological confirmed new oral cancer cases not diagnosed more than a week ago), and with the WHO's ICD-10 oral cancer classification for recruitment of appropriate cases for the study.

After each interview session, additional research assistant who did not conducted the interview went through each section of the questionnaire to look for missing data and if any discrepancies presented, they were clarified immediately with the participants. Further, the completed questionnaire was cross-checked by the principal investigator the following day.

Data collection instrument development

Development or choice of data collection instrument and the corresponding manual is a key step in the study design. The study questionnaire was adopted from the HeNce lifestyle study. HeNce lifestyle study is an international hospital-based case-control study that investigated the aetiology of head and neck cancer in three different countries: Brazil, Canada, and India. The data collection instrument for the above study was validated (Laprise *et al.*,2017; Laprise *et al.,* 2016; TekkePurakkal, *et al.,* 2018) and adapted according to the Bangladeshi context (see Appendix G for the questionnaire). Using a previously validated questionnaire assured the quality of the present study. However, a slight modification was required to suit the current study population and purposes. Details of the modification are discussed in a later section. To ensure the modified version-maintained reliability and validity, a pilot study was conducted, and the instrument was amended accordingly.

Staff training

The aim of staff training is to ensure familiarity with the procedures under each person's responsibility (Szklo and Nieto, 2014). The procedure includes the data collection process, procedures, setting up an appointment for the interview, visiting target departments of the hospital, preparing materials for interviewers etc. (Szklo and Nieto, 2014). The principal investigator and two research assistants, who were trained and registered dentists, conducted all data collection procedures. Additionally, both research assistants had previous experience conducting hospital-based studies. Extensive training was provided to the research assistants by the principal investigator. Each of the research assistants was equipped with a data collection manual to ensure standardisation of data collection to prevent misclassification. To confirm that research assistants were following the standard data collection procedures, some of the interviews were randomly tape recorded with participant permission, which was checked by the study coordinator for adherence to the study protocol.

3.5.6.2 Quality control

The validity of an epidemiological study can be categorised into two main components: internal validity and external validity or generalisability (Rothman, Greenland and Lash, 2012). Selection bias, information bias, and confounders are the key metrics to ensure internal validity.

Selection bias

Selection bias may arise while selecting both cases and controls. However, selection bias occurs less frequently while selecting cases. It happens when exposed cases have higher possibilities of being selected compared to non-exposed cases or vice versa. As suggested by Rego (2010), the inclusion criteria that determine cases must be defined in a way which will assures that all the true cases have the equal likelihood of being selected as cases and need to ensure no false cases are selected. As false case may mispresent the estimate of the measure of association towards the null hypothesis.

To avoid the selection bias for the present study, only biopsy-confirmed new oral cancer cases were recruited. All the new oral cancer cases that arose during the study period were invited to take part in the study. Recruiting all new or incidence cases for the present study also minimised the selection bias. This type of selection bias is also known as Neyman's bias (Souza *et al.,* 2016). Prevalent cases are affected by the duration of the disease and duration is in turn influenced by the treatment, cures and mortality that is associated with the disease. For example, a case-control study could be carried out to look at the association between smoking and risk of stroke. In the study all the cases were selected within 30 days of developing the stroke. If cases who smoked heavily die more frequently, then all the surviving cases that will be recruited for the study would have lower frequency of smoking, therefore will decrease the association between smoking and stroke.

In a case-control study, selection bias may also arise when controls are not representative of the base population from where the cases arose. Thus, the controls should not be chosen based on their *level of exposure* but rather should represent the *distribution of the exposure* in the study population (Souza *et al.,* 2016). Controls were selected from the same hospital as cases, thus produced more confidence in the validity of the study findings (Wacholder *et al.,* 1992). Moreover, the risk of disease was assessed by controlling for the potential confounders (gender and age) during data analysis. The adjustment of the confounders eliminated bias in the crude association between the exposure and the controls' disease. The same adjustment for the confounders was done during the multivariate analysis for the study, which eliminated the potential bias caused by using a particular disease as a source of controls. Another option to reduce the selection bias would be to recruit all the controls with a single disease when the investigator had complete confidence that the disease was unrelated to the exposure of interest. However, rarely there is enough convincing evidence that the assumption of independence of the study exposure and controls' disease is satisfied. Therefore, for the present study, controls were selected from several sources of diseases whose risk factors were not related to the exposure of interest.

Information bias

Due to the retrospective nature of the case-control study, present study may be subject to distinctive types of information bias: recall and interviewer bias (Keogh and Cox, 2014).

Recall bias

Recall bias arises from the differential recall of exposure information by cases and controls. It can arise if cases are likely to provide more or less accurate information about past exposure compared to controls. Using proxies, such as next of kin, can also cause a differential recall. This problem is more common in prevalent cases (Grimes and Schulz, 2002). To minimise the recall bias for this study, the following methodological strategies were applied:

- Only incident cases whose biopsy was confirmed within the previous week were recruited as cases. This allows for more accurate attainment of information, as cases are less likely to change their habits (exposure of interest). Controls were eligible for recruitment if they presented with any disease not related to the exposure of interest and not diagnosed more than one week earlier. By introducing a threshold of one week for both cases and controls, the accuracy of information is expected to be similar between both groups.
- Appropriate control groups were used. The assumption behind this is that the controls are similar to the cases with their concern about the cause of their

disease. Therefore, the accuracy of information between cases and controls is not violated (Hassan, 2005).

- A standardised data collection instrument was used. Information about the exposure was collected in the same way using the same well-structured validated questionnaire to ensure comparable accuracy of information collected.
- Using hospital-based controls was another measure to ensure the comparable accuracy of information between cases and controls (Szklo and Nieto, 2014).
- Using the life grid for interviewing cases and controls also aided in minimising recall bias.

Interviewer bias

Interviewer bias is another common type of information bias in a case-control study, which refers to a systematic difference between how information is solicited, recorded, and interpreted. This bias is more likely to occur when the disease status is known to the interviewer (Pannucci and Wilkins, 2010). To minimise the interviewer bias, interviewer was unaware of whether the participant was a case or a control. To ensure that interviewer is unaware of the case or control status, cases and controls were recruited and interviewed in two steps. In first step, research assistant had selected the cases and controls from target departments and completed the preliminary medical information section. Later, patients were sent to a separate room where principal investigator and other research assistant had conducted interviews. Prior to interview patients were requested not to talk about their disease condition unless asked by the interviewer.

Confounders

The term confounder refers to a situation in which a non-causal association between a given exposure and an outcome is observed because of the influence of a third variable or 'confounding variable' (Szklo and Nieto, 2014). To be considered confounding, the variable must be related to both the risk factor and the outcome under study. From an epidemiological standpoint, confounding is distinct form of bias.

To eliminate the effect of confounders for the present study, two types of measures were taken. The first measure was taken during the study design and before the process of data gathering, and the second measure was taken during the data analysis. For the present study, age and gender were potential confounders, as previous studies suggested that age and gender both are associated with SLT use (exposure of interest) and risk of developing oral cancer (Sreeramareddy *et al.*, 2014a; Khan, Tönnies, and Müller, 2014). To eliminate the confounding effect, cases and controls were age and gender-matched, as restriction eliminates variation in the confounder (Pourhoseingholi, Baghestani, and Vahedi, 2012). Additionally, to detect and eliminate the confounding effect, crude odds ratios from unconditional logistic regression was employed to provide an adjusted result. By examining the difference between the crude and adjusted result, we were able to estimate the effect of confounding (Pourhoseingholi, Baghestani, and Vahedi, 2012). If the difference between the crude and adjusted result was greater than 15%–20%, the potentially confounding factors were regarded as confounder.

3.5.7 Recruitment of study participants

Two dentists were recruited as research assistants (RAs) and were trained by the principal investigator. All the cases for the study were identified from the oral surgery department of the hospital. Controls were selected randomly from the outpatient department of the same hospital. The recruitment of the controls was based on age and sex distribution of the cases. To maintain a good balance of case and controls, a weekly frequency matching list was generated. The research group tried to recruit the required number of controls per cases every week. Any potential study participant was approached by one of the RAs. The purpose of the study was explained to the potential participant as well as the benefits and risks of participating in the study. In addition, the RAs described how confidentiality and anonymity would be maintained and how to withdraw from the study. RAs also answered questions from the study participants. Every participant was provided with a participant information sheet, which was translated into Bengali. Written consent was taken from all the study participants. However, illiterate participants were permitted to use a thumb impression on the consent form, a common practice in Bangladesh for consent, which is also used for voting in the national election. Besides, previous studies conducted in Bangladesh had used the same method to obtain the consent of illiterate participants (Kabir *et al.,* 2016). In these situations, RAs explained the patient information sheet and consent form to the participant in the presence of a witness, and one of the copies of the consent form was given to the study participants.

The main interview was conducted by the principal investigator and one of the RAs who were unaware of whether the participant was case or control.

3.5.8 Study instrument

3.5.8.1 Structured questionnaire

Following the informed consent, face-to-face interviews were conducted with the study participants. The interview lasted approximately 30-45 minutes. A structured questionnaire and life grid were used during the interview.

The questionnaire collected several types of exposures, including socio-demographic information (gender, age, marital status, education, and occupation), weight and height measurement for BMI, behavioural habits (SLT use, tobacco smoking, and alcohol), oral health indicators (partial and complete dentures, frequency and substance used to clean teeth, presence of gum bleeding and ulcers, ad frequency of dental visits), and family history of cancer.

3.5.8.2 Life grid

The life grid approach was incorporated into the interview to enhance the recall of related life events or personal behaviour. It uses a temporal reference line of significant personal and family or external events and dates to prompt and structure the acurate recall of the information of interest (Blane, 1996; Berney and Blane, 1997). The method was developed by Blane (1996) to improve the quality of retrospective data collection. This method helps the study participants to locate past information more accurately by relating it to major events in their past.

A modified version of the life grid was employed to improve the quality of the collected data (See Appendix H). The life grid was introduced at the beginning of the interview. It consisted of four main columns (housing, education or jobs, personal habits, and memorable life events, such as date of marriage, child's birthday, the death of any close person etc.). In addition, the middle line indicated the participant's age. The housing section recorded any important date or the participant's age at the time of any key changes that were related to the residential status. Age could also be related to starting school or attending secondary school, writing an exam, starting a new job or leaving a job. Moreover, participants were asked to record their age when they started smoking or using SLT or alcohol if applicable. Finally, major life events, such as age when they were married, the birth of their first child, the age when there was a significant natural disaster, or significant movement in national politics were recorded before the interview. Once all the important life events were registered in the life grid referring the central age line, a structured interview was conducted by cross-referencing the date and age with the life grid events. If there was any confusion about the age and date in the questionnaire, it was clarified with the study subject with the help of the life grid.

3.5.9 Study measures

3.5.9.1 Outcome variable

Oral cancer was the outcome variable of the study. The definition of oral cancer in this study was based on revised ICD-10 classifications, which included oral cancer of lips, tongue, gums, the floor of the mouth, palate, cheek, vestibule of the mouth, and the retromolar area (WHO, 2014b). Only histologically confirmed new oral cancer cases were recruited for the study. Histologically confirmed cases are regarded as the gold standard for the diagnosis of the malignant lesions (Mehrotra *et al.*, 2012). The outcome variable was a categorical variable based on presence and absence of oral cancer (case/control).

3.5.9.2 Explanatory variables

Socio-demographics

Information regarding gender, age, marital status, education, and occupation was recorded for each study participant and logged as categorical variables. For the purpose of the univariate analysis, age was specified as either below 55 years of age or above. Marital status was recorded as single, married, or divorced, but was dropped during the univariate analysis due to the insufficient variation across the categories (more than 98% of the study participants were married). Regarding education status, participants were categorised into two main categories: no-formal education and formal education. Employment categories were also merged into two categories: in paid employment and unpaid employment/unemployed.

Body mass index (BMI)

To investigate the relationship between BMI and risk of having oral cancer among Bangladeshi subjects, initially height and weight were measured. Later, BMI was measured using the following formula:

BMI = x KG / (y M * y M) (Centres for Disease Control and Prevention, 2018b)

Where, x = bodyweight in KG, y = height in metres.

Later, to explore the independent association BMI was categorised into three main groups: Under-Weight: <18.50; Healthy Weight: 18.50 - 24.99; Over-weight: ≥25.00. However, in the predictive model BMI was considered as continuous variable.

Smokeless tobacco use

For the present study SLT are defined as type of tobacco products that are not burned but predominantly used orally (chewed, sucked, dipped, held in the mouth, etc.) or nasally. Any other chewing products that do not contain tobacco was not considered as SLT. Such as, betel nut, betel leaf, panmasal etc.

For the present study "overall chewing habits" include both SLT and non-tobacco product. "Chewing habits with SLT" only include chewing products that contains SLT and "chewing habits without SLT" includes chewing products that does not contain tobacco.

Study participants who had used SLT for at least one year at any point in their life were considered an "**ever user**" of SLT. Ever users who had stopped taking SLT at least one year prior to the interview were considered a "**past user"** of SLT. Study subjects who had never tried SLT in their lifetime were considered a **"never user".** Ever users who currently use SLT daily or occasionally were considered a **"current user".** Any changes in chewing habits of less than one year were not taken into consideration.

Information related to distinct types of SLT and its ingredients were collected. In this study, betel quid was defined as a combination of betel leaf, areca nut, and slaked lime. Based on the combination of betel quid and SLT, chewing substances were categorised into Zarda only, betel quid with Zarda, betel quid without Zarda, areca nut with Zarda, areca nut without Zarda, Sadapata only, betel quid with Sadapata, gul (Powdered tobacco leaf), pan masala (mixture of tobacco and other flavouring agents), and betel leaf alone. In addition, other possible combinations of SLT were recorded in other's section.

A comprehensive history of SLT was recorded. Respondents were asked to describe their SLT habit by dividing their lifetime consumption into periods based on the homogeneity of type of SLT and frequency of use. One may use different type of SLT in different frequencies at different point in their life. As an example, if a man started chewing BQ at the age of 30 and used two different types (BQ with tobacco and BQ without tobacco), each in three different frequencies (used per day) until the age of 70, his SLT habit history will have six different periods. For each homogeneous period following information was recorded: age of onset, age at quit, frequency of use per day, minutes of each time they chewed SLT. The total duration of use was calculated from the difference between the age of onset and end of the period in years. A cumulative variable was created to understand the lifetime intensity of SLT use based on the information collected. Similar to the calculation of smoking pack-years, for the present study total duration of use in lifetime and frequency of use per day was translated to a variable call "chew-years". Similar to the cigarette packs, 10 SLT portions was considered as one pack. Then frequency of SLT per day was divided by ten to determine the number of packed consumed per day. One chew year was thus defined as ten portions of SLT used per day for one year.

$$\left(\frac{\textit{(Frequency of SLT per day} \times \textit{Total duration of SLT habit in years)}}{\textit{(Number of portions in per SLT pack)}} \right)$$

Tobacco smoking

Cigarettes and bidi are the most common forms of smoked tobacco used in Bangladesh (Nargis, *et al.,* 2015). Another form of tobacco that is smoked by the Bangladeshi population is a water pipe, which is locally known as a 'hukkah' (it includes a tobacco bowl on the top, body, water bowl, and a mouthpiece) (WHO, 2015).

In this study, tobacco smoking was categorised into three main categories: cigarettes (filtered, non-filtered, or hand-rolled), bidi, and water pipes or hukkah. An **"ever smoker"** of cigarettes was defined as an individual who had reported smoking at least one year in his or her lifetime. **"current smoker"** is an individual who had smoked at least 100 cigarettes in their lifetime and currently smokes at the time of the interview. **"past smoker"** is an individual who had smoked 100 cigarettes in their lifetime and gave up smoking completely one year prior to the interview (CDC, 2017b).

Tobacco smoking is a multidimensional process that requires an extensive and precise manner of investigation. The current study collected detailed information related to participant's smoking habits. The information included the total duration of smoking (initiation and cessation age) and total consumption per day. In addition, type of cigarettes (filter, non-filter, and hand-rolled) was also recorded.

In the next phase, a cumulative variable was created to look at the lifetime intensity of smoking. A conventional method used to measure the lifetime intensity of tobacco smoking is called 'pack-year'. This value is calculated by multiplying smoking duration with daily tobacco use (number of cigarettes or bidi per day) (Bernaards *et al.,* 2001). According to the National Cancer Institute, pack-year is "a way to measure the amount a person has smoked over a long period of time. It is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person smoked" (NCI, 2017).

A pack-year of cigarettes will be equal to smoking 20 cigarettes (1 pack) per day for 1 year or two packs of cigarettes for half a year. The pack-year is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years smoked. Initially, years of smoking was calculated by subtracting the cigarette initiation age from the age of cessation or age during the interview if he/she was a current smoker. The number of cigarettes smoked per week and month was converted into number of cigarettes smoked per day. In next step, the number of cigarette packs smoked per day was calculated by dividing the number of cigarettes smoked per day with the number of cigarettes in a pack. In Bangladesh, a standard cigarette pack contains 20 cigarettes. Therefore, the number of cigarettes per day was divided by 20 to determine the number of cigarette packs smoked per day.

Below are some examples to understand the calculation of pack-year:

A person who is 46 years old and reported smoking 25 cigarettes a day for last 10 years and 15 cigarettes a day before that. He or she started smoking at 18 years old and never quit smoking.

The total period of smoking = 28 years.

$25/20 \times 10 = 12.5$ pack-years.

$15/20 \times 18 = 31.5$ pack-years

Therefore, total pack-years in his or her life course would equal 44.

However, for participants who had a history of quitting smoking, the calculation was conducted in the following manner: A person who is 50 years old reported quitting smoking in 2015. However, he reported smoking 10 cigarettes a day for 15 years. Moreover, before that, he had reported smoking 6 cigarettes a day. He started smoking at the age of 15 and quit smoking at the age of 45. He also quit smoking 5 times with an average duration of 3 months.

Therefore, the total duration of smoking (without quitting period) = 30 years.

Total quitting time: $5 \times 3/ 12 = 1.3$ years.

$10/20 \times [15 - (10/30 \times 1.3)] = 7.2$ pack-years

$5/20 \times [15 - (5/30 \times 1.30)] = 3.7$ pack-years.

Therefore, total pack-years for this person would equal 10.9.

The pack-year calculation for filtered and non-filtered cigarettes was later classified in three different categories (never smoker, moderate smoker, and heavy smoker). Subjects who had never smoked cigarettes before formed the never smoker group. The rest of the group was categorised into two groups (moderate and heavy smoker) using median distribution as a cut-off point.

Detailed information about bidi and water pipe/hukkah smoking was also recorded. Bidi and water pipe initiation and cessation age and consumption per day were recorded. To explore the lifetime intensity of bidi smoking, pack-year of bidi was calculated using the same formula above. A standard bidi pack in Bangladesh contains 25 bidis. Therefore, while calculating the pack per day, the number of bidis smoked per day was divided by 25 and multiplied by the total years of use. Due to a limited number of observations in some categories, bidi smoking was categorised into two groups (non-smoker and smoker), as a limited number of respondents contributed to this category.

For example, if a person is 55 years old and reported smoking five bidis per day from the ages of 21 to 34 years, his total bidi smoking period would equal 13 years (34 - 21 = 13). Therefore, the calculation for pack-years would be the following:

$5/25 \times 13 = 2.6$ pack-years

To calculate the pack-year for water pipe smoking, information about the initiation and cessation age and number of pipes full of tobacco smoked per day were recorded. In the next step, the number of pipes per day was divided by five to obtain the equivalent packs per day with the assumption that one pipe full of tobacco is equivalent to four commercial cigarettes (Schlecht, *et al.,* 1999). Later, pack-year was calculated by dividing pack per day with total years of consumption (subtracting cessation age or current age from initiation age).

For example, if a person is 50 years old and reported using one pipe full of tobacco per day from aged 30 to 40 years, the total years of water pipe smoking will be 10 years. Therefore, the pack-year calculation would be the following: $1/5 \times 10 = 2$ pack-years.

Alcohol consumption

The overall prevalence of alcohol drinking is extremely low in Bangladesh. A recent study conducted by Islam *et al.*, (2017) had reported only 5.6% of the total population in Bangladesh had ever drank alcohol. Bangladeshi law had strictly prohibited the consumption of alcohol, and socially unacceptable. Yet, it is available throughout the country and is also produced locally. Therefore, it is possible participants may not disclose their alcohol use. To address this issue, participants were ensured the anonymity and confidentiality of the data provided. A detailed purpose of the study was explained to the participants. To ensure the privacy, interview was conducted in a separate room where only interviewer and the study participant were presented.

Based on the definition of alcohol in Bangladesh, an alcoholic beverage is any liquor that has an alcohol content of ≥0.5%, such as beer (5% volume), wine (12% volume), spirits (40% volume), and locally made toddy (Islam *et al.,* 2017). Detailed information about the of type of alcoholic beverage (locally made alcohol, wine, beer, spirits, or others) were recorded, the unit of drinking (small glass (50ml;1-2oz), medium glass (100ml; 2-3oz), big glass (250ml; 7oz); ½ small bottle (330ml; 1beer); bottle (700-750 ml; 21oz)) was obtained. Additionally, the age of initiation and cessation and total consumption frequency per day, week, and month were also recorded.

However, due to a limited number of responses in this category, this variable was dropped from the disease model. Only eight respondents (1.5%) reported ever drinking alcohol. Details of their drinking pattern will be reported in the results section (seeTable 45).

Oral health indicators

Detailed information of oral health indicators (status of wearing a complete and partial denture, instrument used to clean the teeth, the frequency of cleaning teeth, substance used to clean the teeth, the status of gum bleeding and ulcers or cuts from dentures or teeth, and frequency of dentist visits in the last 20 years) were recorded.

A denture was defined as a complete or partial removable appliance that replaces one or more teeth. Status of using complete and partial dentures was obtained with the site (top, bottom, or both top and bottom). Due to very few numbers of responses, variables related to complete dentures were excluded from the disease model. Status of partial dentures was recorded with its position in the mouth (top, bottom, or both top and bottom).

The instrument used to clean teeth was recorded as toothbrush, fingers, or sticks. The frequency of teeth cleaning was recorded as never, less than once a week, 1-2 times a week, every other day, once a day, or twice or more a day. However, later they were merged into once a day and twice or more a day for the disease model due to the limited number of observations in other categories. The substance to clean teeth was recorded as charcoal, toothpaste, toothpowder, or none. This was later categorised into none or others, toothpaste, and toothpowder due to few observations in some categories. The status of gum bleeding, history of mouth ulcers and frequency of dental visits in the last 20 years was also recorded. However, due to a limited number of responses in the dentist visit category, the variable was later categorised into visit when had pain or never.

Family history of cancer

Detailed information about the family history of cancer was recorded. Respondents were asked if any of their biological family members ever had cancer. Information about their relationship with the person with cancer, survival status, current age or age when they died, type of cancer, and age of diagnosis was also recorded. However, this variable was later dropped due to an insufficient number of respondents in this category.

3.5.10 Data management & analysis

All the data were entered and stored in MS excel 2013. The data analysis was carried out using statistical software SPSS Version: 24. Data analysis was conducted in two steps. In first step simple descriptive analysis was conducted to describe the characteristics of the study subjects and in second step unconditional logistic regression model was used to estimate the association between SLT use and oral cancer risk.

3.5.10.1 Descriptive statistics

To describe the study profile and base line characteristics of cases and controls, descriptive statistics were first performed. Simple descriptive analysis: frequency distribution, percentage and mean were performed to describe the basic characteristics of the study subjects. To compare the distribution of categorical variables across cases and controls cross-tabulation was used. To explore the association between categorical variables Chi-Square test or Fisher-Exact test were performed when appropriate. Simple t-test was used to estimate the difference in mean between cases and controls. The characteristics described in the analysis included: age, gender, education status, work status, BMI, SLT use variables, Smoking variables (cigarettes, bidi and water pipe), Alcohol use variables, Oral health indicators, and family history of cancer.

3.5.10.2 Logistic regression

The association between exposure and outcome variables were estimated with odds ratio (OR) and their 95% Confidence interval and was derived from logistic regression analysis. Logistic regression analysis is a type of statistical method where outcome variable (dichotomous or binary) is associated with explanatory variables by means of logistic functions. The aim of the logistic regression analysis is to treasure the best fitting model (which is also biologically sensible) to describe the relationship between the binary outcome variable and a set of independent variables. With this method the probability of disease occurrence is assessed by fitting the data to the logistic curve. Logistic regression model generates the coefficients to predict the logit transformation of the probability of disease occurrence.

Below is the example of a typical logistic regression model:

$$logit(p) = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + \ldots + b_kX_k$$

(Hosmer, Lemeshow, Sturdivant, 2013)

Here, p is the probability of disease occurrence and $(1 - p)$ is the probability of disease not occurring and the logit transformation is defined as log odds. The log odds of the disease or outcome variable can be presented as a linear function of the independent variables. Shown above. Here, b_0 is the y-intercept and x_1 to x_k are the independent variables. b_1 to b_k are coefficients which indicates the degree of association between outcome variable and explanatory variables.

$$odds = \frac{p}{1-p} = \frac{probability\ of\ presence\ of\ characteristic}{probability\ of\ absence\ of\ characteristic}$$

(Hosmer, Lemeshow, Sturdivant, 2013)

$$logit(p) = \ln\left(\frac{p}{1-p}\right)$$

Below is the example of the logistic regression model for the association between SLT use and oral cancer, and adjusted for age, gender, education status, work status, and smoking history. This model did not consider any interaction term and assumed there is no interaction between the variables.

$$\boldsymbol{log\,i\,t(p) = b_0 + b_1(SLT) + b_2(age) + b_3(gender) + b_4(education\ status) + b_5\ (work\ status) + \ b_6\ (smoking\ status).}$$

Using logistic regression for data analysis was appropriate for the present study since the dependent variable was dichotomous (yes or no) presence of oral cancer or not and allowed simultaneously adjusted for potential confounders (age and gender). An unconditional logistic regression model used for the data analysis and matching variables were included in the model. It is well known that matched case-control study uses traditional matched method of data analysis: conditional logistic regression. However, previous study result showed that the studies that are matched on demographic variables such as: age and gender are loosely matched data and unconditional regression is the appropriate method when the age and gender distribution of the study subjects are not significantly apart (Kuo, Duan, Grady, 2018). Besides, easy to access, straightforward interpretation, preserving unmatched controls were reported as some of the advantages of unconditional logistic regression model (Pearce, 2016). Conditional logistic regression model is considered when the analysis strata are small such as just one case and one control for each stratum whereas when the analysis strata is bigger than 1:1 unconditional logistic regression model is the suitable choice. Thus, for the present study unconditional logistic regression model was used to evaluate the relationship between oral cancer and SLT use and other established risk factors.

The joint effect of SLT use and smoking was evaluated using both multiplicative and additive relative risk models. In each step, the interaction term was included in the model of which the two lower terms were included, and the likelihood ratio statistics was used to evaluate the significance of that additional interaction terms. The interaction term that were tested was "SLT use status (dichotomous)*smoking (dichotomous)" and "cumulative exposure to SLT (dichotomous)* smoking (dichotomous)".

The population attributable fraction (PAF) for Bangladeshi subjects was calculated using the Odds ratio derived from the unconditional logistic regression model and the prevalence of SLT from the national tobacco survey from Bangladesh (WHO, 2017). Following formula was used to calculate the PAF.

PAF = $\frac{[\boldsymbol{P}(\boldsymbol{OR}-\mathbf{1})]}{[\boldsymbol{P}(\boldsymbol{OR}-\mathbf{1})+\mathbf{1}]}$ (Rothman, Greenland and Lash, 2012)

Later, total number of attributable incidence cases (AC) of oral cancer was calculated using the following formula AC = PAF * TC. Here, TC is the total number of annual incident cases of oral cancer. The estimated annual incidence cases of oral cancer was obtained from Global Cancer Observatory, 2018.

3.5.11 Ethical considerations

The study was approved by the Anglia Ruskin University Research ethics committee and the participating hospital (see Appendix I). As mentioned in the earlier section, potential cases and controls were approached by the RAs and the study procedures were explained to the study participants. Written consent was obtained from each participant after handing out and explaining the patient information sheet. Thumb impressions were obtained from participants who were illiterate after reading out and explaining the consent form and patient information sheet by the interviewer with the presence of a witness. One copy of the consent form was provided to the study participants. The consent form and the patient information sheet were translated into Bengali prior to the administration. A copy of the patient information sheet and consent form can be found in the Appendix- J.

Chapter IV. Results

4.1 Adolescent cross-sectional survey Findings

The aim of the adolescent cross-sectional survey was to investigate the practice and pattern of smokeless tobacco (SLT) use as well as the knowledge and perception about its adverse effects among rural Bangladeshi adolescents. In addition, the study determined the predictors of current SLT use.

Students from grade seven to nine from two rural secondary schools in Ramgoti Upazila of Lakshmipur district, Bangladesh were enrolled in the survey during September 2015. In total, 790 students completed the school survey. Both schools and students response rates were 100%. The current chapter presents the findings of the data analysis. The chapter is divided into three major sections. The first section identified the demographic characteristics followed by current practice and pattern of SLT use. The second section identified the knowledge and perception of SLT use and its adverse effects. The last section identified the predictors of current SLT use.

4.1.1 Demographic details

The majority of the survey respondents were male, 63.3% (500) and 36.7% (290) were female students (see Table 19). The main occupation of the student's father was farming 62.4% (493) followed by business 18.4% (145). Most of the study participants' mothers were houseworkers 98.90% (781). Age patterns showed that 40.4% (319) of the students included in the study were 13 years old or younger, 29% (229) were 14 years old and 30.6% (242) were 15 years or older. The mean age of the students was 13.84 ±0.07 years old and the median age was 14. There was no notable difference in mean age of male 13.96 ±0.07 and female students 13.65 ±0.07.

4.1.2 Pattern and practices of smokeless tobacco use

4.1.2.1 Smokeless tobacco uses and its types

Over 90% (715) of the students never tried SLT. Overall, 9.5% (75) students had ever used SLT and 3.7% (29) students were current SLT users. Male had a higher incidence of both ever and current SLT use (See Table 20). When the incidence of SLT use examined across age group, SLT was more prevalent among older adolescents (14 years and above) (see Table 21).

‘Zarda’ was the most favoured form of SLT among both ever 80% (60) and current users (75.9%). Pan masala was the second-most conventional form, overall 20% of ever users and 24.1% of current users reported using it. A similar choice was seen across both genders and age categories (see Table 20 and Table 21).

Table 19: Socio-demographic characteristics of the study participants and smokeless tobacco use

Characteristics	Total% (n)	Ever SLT users	Non-users
Gender			
Male	63.3% (500)	68.0% (51)	62.8% (449)
Female	36.7% (290)	32.0% (24)	37.2% (266)
Age			
13 or younger	40.4% (319)	16.0% (12)	42.9% (307)
14	29.0% (229)	34.7% (26)	28.4% (203)
15 or older	30.6% (242)	49.3% (37)	28.8% (205)
Father’s job			
Farming	62.4% (493)	62.7% (47)	62.4% (446)
Business	18.4% (145)	18.7% (14)	18.3% (131)
Gov. employee	1.4% (11)	8.0% (6)	0.7% (5)
Non-Gov. employee	6.1% (48)	4.0% (3)	6.3% (45)
Doctor	1.3% (10)	1.3% (1)	1.3% (9)
Teacher	3.0% (24)	2.7% (2)	3.1% (22)
Daily labourer	1.9% (15)	0%	2.1% (15)
Unemployed	0.4% (3)	1.3% (1)	0.3% (2)
Others	5.2% (41)	1.3% (1)	5.6% (40)
Mother’s job			
Housework	98.9% (781)	98.7% (74)	98.9% (707)
Gov. employee	0.3% (2)	0%	0.3% (2)
Teacher	0.9% (7)	1.3% (1)	0.8% (6)

Others: Did not mention the father's profession. SLT: Smokeless tobacco

Table 20: Smokeless tobacco use and its types across males and females

Measures	**Male (n)**	**Female (n)**	**Total (n)**	***P-value*** [a]
Ever SLT use [b]				
Never	62.8% (449)	37.2% (266)	100% (715)	0.38
Ever	68.0% (51)	32.0% (24)	100% (75)	
Current SLT use [c]				
No	63.2% (481)	36.8% (280)	100% (761)	0.33
Yes	65.5% (19)	34.5% (10)	100% (29)	
SLT type				
Zarda	76.5% (39)	87.5% (21)	80.0% (60)	0.36
Panmasala	23.5% (12)	12.5% (3)	20.0% (15)	

[a] P-value derived from chi-square test; [b] Tried SLT at least once in their life; [c] Tried SLT at least once in last 30 days

Table 21: Smokeless tobacco use and its types across age categories

Measures	**<14 years old**	**≥14 years old**	**Total (n)**	***P-Value*** [a]
Ever SLT use [b]				**<0.001**
Never	96.2% (307)	86.6% (408)	90.5% (715)	
Ever	3.8% (12)	13.4% (63)	9.5% (75)	
Current SLT use [c]				0.44
No	99.1% (316)	9.5% (445)	96.3% (761)	
Yes	0.90% (3)	5.5% (26)	3.7% (29)	
SLT Type				0.43
Zarda	91.7% (11)	77.8% (49)	80.0% (60)	
Panmasala	8.3% (1)	22.2% (14)	20.0% (15)	

[a] P-value derived from chi-square test; [b] Tried SLT at least once in their life; [c] Tried SLT at least once in last 30 days

4.1.2.2 Smokeless tobacco initiation age

Regarding the age of onset, students started using SLT as early as seven years old or younger 5.3% (4). When the age of onset was observed by gender, males 35.3% (18) tried SLT at an earlier age (10-11 years old) compared to females 41.7% (10) (12-13 years old) (see Table 22) and the association was statistically significant, p=0.03.

Table 22: Smokeless tobacco initiation age across gender

Measures	Male	Female	Total (n)	***P-Value*** [a]
Age at SLT initiation				**0.03**
≤ 7 Years	7.8% (4)	0%	5.3% (4)	
8 - 9 years	3.9% (2)	8.3% (2)	5.3% (4)	
10 - 11 years	35.3% (18)	25.0% (6)	32.0% (24)	
12 - 13 years	31.4% (16)	41.7% (10)	34.7% (26)	
14 - 15 years	21.6% (11)	25.0% (6)	22.7% (17)	
Did not use	62.7% (32)	58.3% (14)	61.3% (46)	

[a] *P-value obtained from Fisher-exact test*

Relating to the SLT use status, majority current and former users reported trying SLT at the age between 12 to 13 years old (see Table 23).

Table 23: Smokeless tobacco initiation age across smokeless tobacco use status

Measures	Past users	Current users	Total (n)	P-Value [a]
Age at SLT initiation				0.56
≤ 7 Years	8.7% (4)	0%	5.3% (4)	
8 - 9 years	4.3% (2)	6.9% (2)	5.3% (4)	
10 - 11 years	32.6% (15)	31.0% (9)	32.0% (24)	
12 - 13 years	34.8% (16)	34.5% (10)	34.7% (26)	
14 - 15 years	19.6% (9)	27.6% (8)	22.7% (17)	

[a] *P-value derived from Fisher-exact test*

4.1.2.3 Smokeless tobacco dependency

When inquired about the number of days SLT used in last 30 days (only current users), majority current users 24.0% (18) used it only 1 to 2 days. Among gender, girls reported using SLT more days compared to boys, 20.8% (5) females compared to 5.9% (3) males reported using it 3 to 5 days in last month Table 24).

Users were questioned about the number of times SLT used per day in the last 30 days (current users), only 34.5% (10) reported using SLT at least once per day. Among gender, males had a higher frequency of SLT use per day compared to females (see Table 24).

Students were asked if they had a strong desire to use SLT first thing in the morning, only 9.3% (7) students reported sometimes felt to use SLT first thing in the morning. When examined across gender, more females 12.5% (3) compared to males, 7.8% (4) thought to use SLT first thing in the morning (see Table 24).

Table 24: Distribution of smokeless tobacco use pattern and dependency across gender

Measures	Males (n)	Females (n)	Total (n)	***P - value***
Number of days SLT use				
Did not use	62.7% (32)	58.3% (14)	61.3% (46)	0.28 [b]
1 to 2 days	27.5% (14)	16.7% (4)	24.0% (18)	
3 to 5 days	5.9% (3)	20.8% (5)	10.7% (8)	
20 to 29 days	0.0%	4.2% (1)	1.3% (1)	
All 30 days	3.9% (2)	0.0	2.7% (2)	
Frequency per day (current)				
Less than once per day	63.2% (12)	70.0% (7)	65.5% (19)	0.71 [a]
At least once per day	36.8% (7)	30.0% (3)	34.5% (10)	
Use SLT, first thing in the morning				
No	90.2% (46)	87.5% (21)	89.3% (67)	0.78 [b]
Yes sometimes	7.8% (4)	12.5% (3)	9.3% (7)	
Yes always	2.0% (1)	0.0	1.3% (1)	
The desire to use it again				
Never	80.4% (41)	91.7% (22)	84.0% (63)	0.88 [a]
Within 60 minutes	9.8% (5)	8.3% (2)	9.3% (7)	
1 to 2 hours	5.9% (3)	0.0	4.0% (3)	
1 to 3 days	2.0% (1)	0.0	1.3% (1)	
4 Days or more	2.0% (1)	0.0	1.3% (1)	

SLT Smokeless Tobacco, [a] Chi-Square Test, [b] Fisher-Exact test, Significant results are bold

Regarding a strong craving to use SLT again just after using it, only 13.3% (10) participants wanted to use SLT again within two hours or less. Regarding gender difference, 15.7% (8) male compared to 8.3% (2) female students acknowledged getting the urge to use it further within 2 hours or less (see Table 24).

4.1.3 Outcome expectancies

"Outcome expectancy" (One of the constructs of SCT) was measured by examining the reasons for SLT use. Many students 36.7% (29) did not know the reason for using SLT. Among those mentioned a reason, pleasure was the most often quoted reason for SLT use 26.7% (20). Regarding gender, only male participants 9.3% (5) stated using SLT due to peer pressure (see Table 25).

Table 25: Reason for using smokeless tobacco across gender

Measures	Male (n)	Female (n)	Total (n)	*P-value* [a]
Reasons				
Taste	13.0% (7)	12.0% (3)	12.7% (10)	0.47
Smell	5.6% (3)	4.0% (1)	5.1% (4)	
Pleasure	27.8% (15)	28.0% (7)	26.7% (20)	
Feels better	0.0% (0)	4.0% (1)	1.3% (1)	
Friend does	9.3% (5)	0.0% (0)	6.3% (5)	
Do not know	37.0% (20)	36.0% (9)	36.7% (29)	
Other reason	7.4% (4)	16.0% (4)	10.1% (8)	

[a] *Fisher-exact test*

4.1.4 Perceived barrier

Students were asked whether they preferred to quit SLT now. Overall, 89.7% (26) of current users wished to stop using SLT now. Among current users, 94.7% (18) males and 80.0% (8) females wanted to quit SLT (see Table 26).

Regarding the attempt to quit SLT in the past 12 months, overall 34.5% (10) current SLT users tried to stop SLT but failed. Amongst both genders, the male had a higher rate of failure in quitting SLT compared to the female students [42.1% (8) vs

20.0% (2)]. Students were inquired about their perception of quitting SLT, 59% (466) of the students thought it is not hard to quit and this percentage was higher among males (see Table 26).

Table 26: Perceived barrier of quitting smokeless tobacco across gender

Measures	Male (n)	Female (n)	Total (n)	*P-value*
Want to stop (Current users)				
Yes	94.7% (18)	80.0% (8)	89.7% (26)	0.58[a]
No	5.3% (1)	20.0% (2)	10.3% (3)	
Tried to stop (Current users)				
Tried but unsuccessful	42.1% (8)	20.0% (2)	34.5% (10)	0.13 [a]
Did not try to quit	57.9% (11)	80.0% (8)	65.5% (19)	
Difficulty quitting SLT				
No	60.0% (300)	57.2% (166)	59.0% (466)	0.45 [a]
Yes	40.0% (200)	42.8% (124)	41.0% (324)	
Source of help to quit (Current user)				
A programme	0.0% (0)	0.0% (0)	0.0% 0)	0.54 [b]
Friend	42.1% (8)	0.0%	27.6% (8)	
Family	31.6% (6)	80% (8)	43.8% (14)	
No help	26.3% (5)	20.0% (2)	24.1% (7)	
Health warnings				
No	47.1% (24)	41.7% (10)	45.3% (34)	0.80 [b]
Yes, did not care	17.6% (9)	41.7% (10)	25.3% (19)	
Yes, thought of quitting	35.3% (18)	16.7% (4)	29.3% (22)	

[a] Chi-Square Test, [b] Fisher-Exact test

4.1.5 Cues to action

Referring to the support to quit SLT, no one received advice from a programme or professionals. Family and friends were the main sources of aid for those reported getting help to quit (see Table 26).

Table 26 illustrates that majority SLT users 45.3% (34) did not see any anti-tobacco message on SLT packages. Only 29.3% (22) mentioned seeing the health warning label of SLT packages and that led them to think about quitting SLT.

4.1.6 Access and availability

Table 27 shows most students who tried to buy SLT in the past 30 days got it from someone else 41.4% (12) and 34.4% (10) obtained it from stores and shops. Getting SLT from someone was the dominant sources of SLT for both male 38.1% (8) and female students 50% (4).

Table 27: Availability and accessibility of smokeless tobacco across gender

Measures	Male (n)	Female (n)	Total (n)	***P-value***
Source of SLT				
School Shop	4.8% (1)	12.5% (1)	6.9% (2)	0.52 [a]
Street Vendor	14.3% (3)	0.0%	10.3% (3)	
Someone else	38.1% (8)	50.0% (4)	41.4% (12)	
Store near house	19.0% (4)	0.0%	13.8% (4)	
Got it another way	23.8% (5)	25.0% (2)	24.1% (7)	
On the way to school	0.0%	12.5% (1)	3.4% (1)	
Refuse to sell SLT				
No	62.5% (10)	71.4% (5)	65.2% (15)	0.68 [b]
Yes	37.5% (6)	28.6% (2)	34.8% (8)	

[a] *P-value derived from Fisher-exact test;* [b] *P-value derived from Chi-square test*

To assess the efficiency of tobacco control law which prohibited selling SLT to the minors, respondents were asked whether anyone refused to sell SLT because of their age, more than 60% ever SLT users and 86% (12) current SLT users were able to buy SLT without any restriction. A Fisher-Exact Test was conducted between current SLT use and status of refusal because of age. There was a significant statistical association between both variables, $p = 0.02$.

4.1.7 Self-efficacy

The overall susceptibility to SLT use was 2.8% (22) when offered by friends and was significantly associated with ever SLT use (see Table 28). Specifically, 8% (6) of ever SLT users compared to 2.2% (16) of never users were likely to use SLT if offered by their friend (p = 0.01).

Table 28: Self-efficacy across gender and smokeless tobacco use status

Measures	**Male (n)**	**Female (n)**	**Total (n)**	***P*-value [a]**
If offered by a Friend				0.26
No	97.8% (489)	96.2% (279)	97.2% (768)	
Yes	2.2% (11)	3.8% (11)	2.8% (22)	
Measures	**Never user (n)**	**Ever users (n)**	**Total (n)**	***P-value* [a]**
If offered by a Friend				
No	97.8% (699)	92% (69)	97.2% (768)	**0.01**
Yes	2.2% (16)	8.0% (6)	2.8% (22)	

[a] *P-value derived from chi-square test*

4.1.8 Knowledge about the adverse effects of smokeless tobacco use

Knowledge about the harmful effects of SLT was measured with three constructs of the HBM (perceived susceptibility, perceived severity, and perceived benefits).

4.1.8.1 Perceived susceptibility

The overall knowledge about the harmfulness of SLT use was good among respondents. Majority adolescents 75.6% (597) thought SLT use is bad for health (see Table 29). However, 21.2% of survey participants did not know whether SLT use is bad or good for health. Among gender, more females 26.2% (76) compared to males 18.6% (93) did not know whether SLT use is good or bad for their health. As assessed by Fisher-Exact test, it was statistically significant, $P = 0.01$ (see Table 30).

When examined across SLT use status, never users had greater knowledge in this category compared to ever users where, 4% ever users compared to never users 0.60% thought SLT use is good for health. The association was statistically significant, where *p-value* was 0.02 (see Table 29).

Table 29: Overall perception of smokeless tobacco use across gender and user status

Measures	Male (n)	Female (n)	Overall (n)	*P-Value*
Do you think SLT use is				**0.01 [a]**
Do not Know	18.6% (93)	26.2% (76)	21.4% (169)	
Good for health	0.6% (3)	1.4% (4)	0.9% (7)	
Neither good or bad	1.6% (8)	3.1% (9)	2.2% (17)	
Not good	79.2% (396)	69.3% (201)	75.6% (597)	
Measures	**Never users (n)**	**Ever users(n)**	**Overall (n)**	***P-Value***
Do you think SLT use is				**0.02 [a]**
Do not Know	21.5% (154)	20.0% (15)	21.4% (169)	
Good for health	0.6% (4)	4.0% (3)	0.9% (7)	
Neither good or bad	2.2% (16)	1.3% (1)	2.2% (17)	
Not good	75.7% (541)	74.7% (56)	75.6% (597)	

[a] *fisher-exact test*

Students were further asked about the several common adverse effects of SLT and its chemical contents to consider their perceived susceptibility. When respondents were asked whether SLT causes white patches in the mouth, 29.2% (231) did not know SLT causes white lesions. More Females compared to males thought SLT use does not cause white patches in the mouth (18.6% vs 9.2%). The association was statistically significant, $p < 0.001$ (see Table 30). When looked by SLT use status, 28.1% (201) never users and 40% (30) ever users did not know SLT causes white patches in the mouth (see Table 31).

Table 30: Knowledge about the harmful effects and contents across gender

Measures	Male (n)	Female (n)	Overall (n)	*P-Value[a]*
SLT causes white patches				**<0.001**
No	9.2% (46)	18.6% (54)	12.7% (100)	
Yes	59.2% (296)	56.2% (163)	58.1% (459)	
Do not know	31.6% (158)	25.2% (73)	29.2% (231)	
SLT cause oral cancer				
No	8.8% (44)	13.1% (38)	10.4% (82)	0.08
Yes	66.8% (334)	60.0% (174)	64.3% (508)	
Do not know	24.4% (122)	26.9% (78)	25.3% (200)	
SLT cause gum diseases				
No	8.8% (44)	15.9% (46)	11.4% (90)	**0.01**
Yes	64.8% (324)	58.6% (170)	62.5% (494)	
Do not know	26.4% (132)	25.5% (74)	26.1% (206)	
SLT causes heart disease				
No	9.6% (48)	19.7% (57)	13.3% (105)	**<0.001**
Yes	67.2% (336)	51.0% (148)	61.3% (484)	
Do not know	23.2% (116)	29.3% (85)	25.4% (201)	
SLT contain nicotine				
No	9.8% (49)	12.1% (35)	10.6% (84)	**<0.001**
Yes	62.2% (311)	47.6% (138)	56.8% (449)	
Do not know	28.0% (140)	40.3% (117)	32.6% (257)	

[a] Fisher-Exact test

Regarding oral cancer, majority students 64.3% (508) knew SLT causes oral cancer. Yet, 25.3% (200) participants did not know, and 10.4% (82) thought SLT use does not cause mouth cancer. When looking at gender, more females compare to males thought SLT use does not cause oral cancer (13.1% vs 8.8%). When compared across SLT use status, there was a considerable disparity between never and ever users who did not know that SLT causes oral cancer (24.1% vs 37.3%). The association was statistically significant, $p = 0.01$ (see Table 31).

Table 31: Knowledge about the harmful effects and contents across smokeless tobacco use status

Measures	Never user (n)	Ever user (n)	Overall (n)	*P-Value*[a]
SLT causes white patches				0.09
No	12.9% (92)	10.7% (8)	12.7% (100)	
Yes	59.0% (422)	49.3% (37)	58.1% (459)	
Do not know	28.1% (201)	40.0% (30)	29.2% (231)	
SLT cause oral cancer				
No	11.0% (79)	4.0% (3)	10.4% (82)	**0.01**
Yes	64.9% (464)	58.7% (44)	64.3% (508)	
Do not know	24.1% (172)	37.3% (28)	25.3% (200)	
SLT cause gum diseases				
No	12.4% (89)	1.3% (1)	11.4% (90)	**<0.001**
Yes	64.1% (458)	48.0% (36)	62.5% (494)	
Do not know	23.5% (168)	50.7% (38)	26.1% (201)	
SLT cause heart disease				
No	14.1% (101)	5.3% (4)	13.3% (105)	**0.003**
Yes	62.0% (443)	54.7% (41)	61.3% (484)	
Do not know	23.9% (171)	40.0% (30)	25.4% (201)	
SLT contain nicotine				
No	10.6% (76)	10.7% (8)	10.6% (84)	**0.003**
Yes	58.6% (419)	40.0% (30)	56.8% (449)	
Do not know	30.8% (220)	49.3% (37)	32.5% (257)	

[a] *Fisher-exact test*

Respondents were further questioned if SLT causes gum diseases. The majority students 62.5% (494) answered yes. However, more females than males thought SLT use does not cause gum diseases (15.9% vs 8.8%) and the association was statistically significant, $p = 0.01$ (see Table 30). Among SLT users and non-users, there was a considerable difference where 50.7% (38) ever users compared to 23.5% (168) never users did not know this fact. The association was statistically significant, $p < 0.001$ (see Table 31).

Participants were asked if SLT causes heart diseases. The majority students 61.3% (484) answered yes and 25.4% (201) students did not know. Overall, females were less aware than males of the risk of heart disease related to SLT use. More females than males thought SLT does not cause heart diseases (19.7% female vs 9.6% male). The association was statistically significant ($p < 0.001$). Regarding SLT use status, a significant proportion of ever users 40.0% (30) compared to 23.9% (171) never users did not know that SLT uses cause heart diseases. The association was statistically significant, $p = 0.003$ (see Table 31)

Regarding the harmful content of SLT, 43.1% students either did not know or thought SLT does not contains nicotine. When compared across gender, higher percentage of female students 12.1% (35) compared to 9.8% (49) male students thought SLT does not contain nicotine. The association was statistically significant ($P < 0.001$) (see Table 30). Across the SLT use status, there was a marked difference between never and ever users in this category; 49.3% (37) ever users compared to 30.8% (220) never users did not know SLT contains nicotine. The association was statistically significant, *p = 0.003* (see Table 31).

4.1.8.2 Perceived benefits

Students were asked if there is any benefit of SLT use to their health; 98.2% (776) responded no and only 1.8% (14) answered yes. The answer did not vary across gender. However, there was a statistically significant association between never users and ever users, where 5.3% (4) ever users compared to 1.4% (10) never users thought SLT use had benefit to their health (see Table 32).

Table 32: Perceived benefits across gender and smokeless tobacco use status

Measures	**Male (n)**	**Female (n)**	**Overall (n)**	***P-Value[a]***
Are there benefits of SLT to your body and health?				0.23
No	97.8% (489)	99.0% (287)	98.2% (776)	
Yes	2.2% (11)	1.0% (3)	1.8% (14)	
Measures	**Never users (n)**	**Ever users(n)**	**Overall (n)**	***P-Value[a]***
Are there benefits of SLT to your body and health?				**0.03**
No	98.6% (705)	94.7% (71)	98.2% (776)	
Yes	1.4% (10)	5.3% (4)	1.8% (14)	

[a] *Chi-Square test*

4.1.8.3 Perceived severity

Regarding the relative harm of SLT use, a majority student 57.8% thought SLT use is less harmful compared to smoking tobacco. More male 29.6% (148) compared to 18.6% (54) female thought SLT use was less harmful compared to ST. The association was statistically significant (*p-value* 0.002*)*. Among SLT use status, never users had a better knowledge in this category compared to ever users. More ever users 72% compared to 56.2%n ever users either did not know or thought SLT is less harmful than smoking tobacco. The association was statistically significant, as estimated by Fisher-exact test *p = 0.02* (see Table 33).

Table 33: Perceived severity across gender and smokeless tobacco use status

Measures	Male (n)	Female (n)	Overall (n)	*P-Value[a]*
Does SLT cause less harm compared to ST?				**0.002**
No	39.0% (195)	47.9% (139)	42.3% (334)	
Yes	29.6% (148)	18.6% (54)	25.6% (202)	
Do not know	31.4% (157)	33.4% (97)	32.2% (254)	
Measures	**Never users (n)**	**Ever users(n)**	**Overall (n)**	***P-Value***
Does SLT cause less harm compared to ST?				**0.02**
No	43.8% (313)	28.0% (21)	42.3% (334)	
Yes	24.6% (176)	34.7% (26)	25.6% (202)	
Do not' know	31.6% (226)	37.3% (28)	32.2% (254)	

[a] *Fisher-exact test*

4.1.8.4 Knowledge index across various factors

Table 34 illustrates the knowledge category across various factors. Respondents were categorised into three main groups based on the overall score distribution (poor knowledge, average knowledge, good knowledge). Overall, 54.2% (428) of respondents had a good knowledge about the disastrous effects of SLT. The majority of never SLT users (55.4%;396) scored in the good knowledge category compared to ever users (42.7%; 32). Male respondents were more aware of SLT use hazards (56%) compared to females (51%) (see Table 34). Knowledge was also significantly associated with respondent's ability to refuse SLT if offered by friend, 55.2% (424) of respondents who would refuse to use SLT if offered by a friend had the good knowledge compared to 18.2% (four) of those who would use SLT ($p = 0.003$). In addition, respondents who thought quitting SLT is easy had the poor knowledge 9.6% (31) compared those who thought the opposite ($p =< 0.001$).

Table 34: Knowledge category across various factors.

Category	Poor Knowledge	Average Knowledge	Good Knowledge	***P- Value***
SLT use status				
Never users	15.9% (114)	28.7% (205)	55.4% (396)	0.05*
Ever users	25.3% (19)	32.0% (24)	42.7% (32)	
Current users	27.6% (8)	24.1% (7)	48.3% (14)	0.28*
Gender				
Male	14.6% (73)	29.4% (147)	56.0% (280)	0.08*
Female	20.7% (60)	28.3% (82)	51.0% (148)	
Age				
14 < years	18.5% (59)	26.3% (84)	55.2% (176)	0.32*
≥ 14 years	15.7% (74)	30.8% (145)	53.5% (252)	
Fathers profession				
Farmer	18.2% (93)	29.5% (151)	52.3% (267)	0.25*
Other	14.3% (40)	28.0% (78)	57.7% (161)	
Age of onset				
≤ 7 years	25.0% (1)	0.0%	75.0% (3)	0.17**
8 - 9	0.0%	0.0%	100.0% (4)	
10 - 11	20.8% (5)	33.3% (8)	45.8% (11)	
12 - 13	23.1% (6)	46.2% (12)	30.8% (8)	
14 - 15	41.2% (7)	23.5% (4)	35.3% (6)	
Want to quit				
Yes	30.2% (13)	34.9% (15)	34.9% (15)	0.54*
No	12.5% (1)	37.5% (3)	50.0% (4)	
Tried to quit last year				
Yes	9.5% (2)	38.1% (8)	52.4% (11)	0.49*
No	22.2% (12)	29.6% (16)	48.1% (26)	
Health warning				
Yes	29.3% (12)	43.9% (18)	26.8% (11)	**0.007***
No	20.6% (7)	17.6% (6)	61.8% (21)	
If offered by a friend				
Yes	27.3% (6)	54.5% (12)	18.2% (4)	**0.003***
No	16.5% (127)	28.3% (217)	55.2% (424)	
Difficult to quit				
Yes	9.6% (31)	32.4% (105)	58.0% (188)	**<0.001***
No	21.9% (102)	26.6% (124)	51.5% (240)	

**Chi-Square Test, ** Fisher-Exact test, Significant results are bold*

4.1.9 Predictors of current smokeless tobacco use

4.1.9.1 Univariate logistic regression result

Logistic regression was applied to determine independent predictors of current SLT use. Binominal logistic regression was used as the dependent variable (current SLT use) was dichotomous (Yes/No). Univariate logistic regression was first performed as an initial screening to establish variables that can be used to predict current SLT behaviour (see Appendix F). Akaike information criterion (AIC) was further obtained for each variable. Some variables were presented with different cut-off values. Each of these then was assessed and the variable with the lowest AIC was included in the final model. Only variables that were significant in the initial screening (univariate logistic regression) were included in the multivariate regression model.

The univariate logistic regression analysis indicated that age was significantly associated with current SLT use. Respondents who were 14 years and older were six times more likely to be current SLT users compared to those less than 14 years old [OR = 6.15, 95%CI: 1.85-20.51, p = 0.003]. Respondents whose father's profession was other than farming were 0.37 times less likely to be current SLT users compared to those with farmer [OR= 0.37, 95% CI: 0.14 – 0.98, p = 0.04]. Respondents who were not refused to buy SLT because of their age were 12 times more likely to be current SLT users [OR= 12.0, 95% CI: 1.56-92.29, p= 0.017]. However, the estimate was not precise as certainly few observations in this category and dropped for the multivariate model because of poor model fit. Regarding the 'Self-efficacy' Students who would use SLT if offered by a friend were six times more likely to be current users compared to those who would not [OR- 6.60, 95%CI: 2.08 -20.95, p = 0.001]. In addition, the perception regarding the difficulty of quitting was also associated with current SLT use. Students who felt it is easy to quit SLT are over two times likely to be current SLT users [OR- 2.75, 95%CI: 1.11-6.84, p= *0*.02]. Respondents who considered there is a health benefit of SLT use were five times more likely to be current SLT users [OR = 5.05, 95%CI: 1.31-18.31, p = 0.014]. Besides, students who thought SLT is less harmful compared to smoking tobacco were more than three times likely to be current SLT users [OR = 3.73, 95%CI: 1.41-9.90 p = 0.008].

Table 35: Univariate analysis of predictors of current smokeless tobacco use

Categories	Crude OR [a]	95% CI of OR	*P-value*	AIC
Gender (Personal characteristics)				252.53
Male	Reference	Reference	0.80	
Female	0.90	0.41-1.97		
Father's profession (Personal characteristics)				247.78
Farmer	Reference	Reference	**0.04**	
Others	0.37	0.14-0.98		
Age (Personal characteristics)				239.14
<14 years old	Reference	Reference	**0.003**	
≥ 14 years old	6.15	1.85-20.51		
Reason for using SLT (outcome expectancies)				
Do not Know	Reference	Reference	0.07	253.12
Had a reason	0.41	0.16-1.07		
Refuse to sell SLT because of your age (Environmental factors)				
Yes	Reference	Reference	**0.02**	252.39
No	12.0	1.56-92.29		
If someone offered you SLT, would you use it? (Self-efficacy)				245.28
No	Reference	Reference	**0.001**	
Yes	6.60	2.08-20.95		
Noticed any health warning on the SLT packages (Cues to action)				252.98

Categories	Crude OR [a]	95% CI of OR	P-value	AIC
No	Reference	Reference	0.58	
Yes	1.30	0.51-3.31		
Did you receive help to quit SLT? (Cues to Action)			0.26	252.25
No	Reference	Reference		
Yes	2.25	0.55-9.21		
Is it difficult to quit? (Perceived barriers)				247.00
Yes	Reference	Reference	**0.02**	
No	2.75	1.11-6.84		
Do you think SLT use is good for health? (Perceived benefits)				252.88
No	References	Reference	0.11	
Yes	6.87	0.66-71.21		
Are there any benefits of using SLT? (Perceived benefits)				248.21
No	Reference	Reference	**0.01**	
Yes	5.05	1.31-18.31		
Does SLT cause less harm to health compared to ST? (Perceived severity)				243.67
No	Reference	Reference	**0.008**	
Yes	3.73	1.41-9.90		
Does SLT cause white patches in the mouth? (Perceived susceptibility)				251.29
Yes	Reference	Reference	0.07	

Categories	Crude OR [a]	95% CI of OR	P-value	AIC
No	1.54	0.73-3.24		
Can SLT cause oral cancer? (Perceived susceptibility)				251.65
Yes	Reference	Reference	0.34	
No	1.49	0.65-3.42		
Does SLT cause gum diseases? (Perceived susceptibility)				252.40
Yes	Reference	Reference	0.66	
No	1.18	0.56-2.52		
Does SLT cause heart diseases? (Perceived susceptibility)				251.34
Yes	Reference	Reference	0.26	
No	1.53	0.73-3.22		
Does SLT contain nicotine? (Perceived susceptibility)				249.45
Yes	Reference	Reference	0.07	
No	1.96	0.92-4.17		

4.1.9.2 Multivariate logistic regression result

After incorporating the significant variables from univariate analysis into the model, only fathers' job became non-significant while the remaining variables were still significant predictors of current SLT use.

Multivariate analysis results indicated that older adolescents (14 years or over) were six times more likely to be current users than those younger adolescents (less than 14 years old) (P=0.003) holding the other variables constant. Self-efficacy was one of the significant predictors of current SLT use. Respondents who would use SLT if offered by a friend were nearly six times likely to be current SLT users compared those who would not use [OR = 5.79, 95% C. I = 1.62-20.62, $p = 0.007$]. Both perceived barriers and perceived benefits were significant predictors of current SLT. Both odds ratios exceeded three (see Table 36). Perceived severity was also a strong predictor of current SLT use. Respondents who thought SLT was less harmful (compared to smoking tobacco) was more than two times likely to be current SLT users compared to those who did not [OR = 2.78, 95% CI = 1.01-7.61, $p = 0.04$]. For the final model diagnostic please see the Appendix F.

Table 36: Multivariate analysis of predictors of current smokeless tobacco use

Categories	*B*	*SE B*	*Wald* χ^2	Odds ratio	95% CI of OR	P-value
Father's profession (Demographic factors)						
Farmer	Reference	Reference	Reference	Reference	Reference	0.08
Others	-0.88	0.51	2.90	0.42	0.15-1.14	
Age (Demographic factors)						
<14 years old	Reference	Reference	Reference	Reference	Reference	**0.003**
≥ 14 years old	1.89	0.63	9.06	6.59	1.93-22.50	
If someone offered you SLT, would you use it? (self-efficacy)						
No	Reference	Reference	Reference	Reference	Reference	**0.007**
Yes	1.76	0.65	7.34	5.79	1.62-20.62	
Is it difficult to quit? (Perceived barrier)						
Yes	Reference	Reference	Reference	Reference	Reference	**0.02**
No	1.19	0.49	5.98	3.31	1.27-8.65	
Are there any benefits of using SLT? (Perceived benefits)						
No	Reference	Reference	Reference	Reference	Reference	**0.03**
Yes	1.54	0.71	4.73	4.67	1.16-18.67	
Does SLT cause less harm to health compared to ST? (Perceived severity)						
No	Reference	Reference	Reference	Reference	Reference	**0.04**
Yes	1.02	0.51	3.96	2.78	1.01-7.61	

4.2 Hospital-based case-control study findings

A hospital-based case-control study was conducted to establish the association between SLT use and oral cancer risk among Bangladeshi adults. Additionally, other known or putative risk factors for oral cancer in the study population were examined. This section of the chapter presents the findings of the case-control study. The chapter is presented in four major sections. The first section demonstrates the case and control participation, general characteristics of the non-participants. Additionally, the cancer site and histopathological grading of the recruited cases and underlying conditions of controls hospital visit, or admission is also explored in this section. The second section presents findings from the descriptive analysis includes- socio-demographic characteristics of the case and controls and distribution of known and putative risk factors of oral cancer. Third section of the chapter identifies the odds ratios for oral cancer of known and possible risk factors. The last section focuses on exploring the association between SLT use and oral cancer risk and population attributable risk associated with SLT use.

4.2.1 Case and control participation

In this hospital-based case-control study, 169 incident (new cases) oral cancer cases were recruited during the July 2015 to December 2015. There were 182 new oral cancer cases identified during the study period. Among them nine patients declined to take part in the study due to time constraints. These patients were referred to another cancer hospital for further treatment. The study site only provides surgical treatment, other cancer care treatments such as chemo and radiotherapy patients are transferred to nearest cancer hospital. Another four patients were unable to provide consent because of mental conditions. Overall, case participation rate was 92.86%.

A total of 338 controls were selected from the outdoor departments of the same hospital with a case and control ratio of 1:2. Controls were frequency matched for gender and age (+/- five years old). Only nine patients declined to participate in the study. Table 37 illustrates the distribution of non-participant cases and controls. Non-participation rate was higher among female cases and male controls. Marital status and age distribution were similar among participant cases, controls and non-participants cases and controls (see Table 37 and Table 41). The current SLT incidence among non-participant cases and controls were 76.9% and 44.4% respectively. The ever-smoking incidence among non-participant cases and controls were 23.1% and 22.2%.

Table 37: Characteristics of non-participants

Characteristics	Non-participant cases (%)	Non-participant controls (%)
Gender		
Male	5 (33.4)	6 (66.7)
Female	8 (61.6)	3 (33.3)
Marital status		
Single	0 (0)	1 (10.0)
Married	13 (100)	8 (90.0)
Age		
<55 years old	6 (46.1)	4 (44.4)
≥55 years old	7 (53.9)	5 (55.6)
SLT use status		
None	1 (7.7)	2 (22.2)
Current users	10 (76.9)	4 (44.4)
Past users	2 (15.4)	3 (33.4)
Smoking status		
Never smoker	10 (76.9)	7 (77.8)
Ever smoker	3 (23.1)	2 (22.2)

4.2.2 Distribution of cases according to clinical and histopathological characteristics

As seen on Table 38 left buccal mucosa was the most common site for cancerous lesions with 62 cases (36.7%), followed by right buccal mucosa 54 (32%) and gum with 20 cases (11.8%). The least common site was left side and middle of the tongue (one case each) followed by the lower lip and floor of the mouth, two cases each.

Table 38: Distribution of cases according to the cancer site

ICD	Topographic Site	n	%
(C03)	Gums	20	11.8%
(C00.4)	Lower Lip	2	1.2%
(C06)	Left buccal mucosa	62	36.7%
(C06)	Right buccal mucosa	54	32.0%
(C02)	Left side of the tongue	1	0.6%
(C02)	Middle of the tongue	1	0.6%
(C01)	Back of the tongue	3	1.8%
(C04)	Floor of the mouth	2	1.2%
(C05)	Soft palate	5	3.0%
(C06)	Oral cancer with overlapping regions	19	11.2%
	Total	169	100.0%

Histopathological grading or Broder's classification of tumour staging is a traditional pathological tool. Early study results described that histopathological grading of cancer is an effective tool in relation to prognostic value (Edmundson, 1948). Besides, it is a common practice in the staging of oral malignant tumours (Lindenblatt *et al.,* 2012). Also, it is a frequently used method in public hospitals of developing countries where the TNM (Tumour Nodes Metastasis) system is associated with higher costs. The grading system is based on morphological characteristics of the tissue such as level of keratinisation, the pattern of invasion, the number of mitoses, nuclear polymorphism. Based on the above characteristics, there are four different grades of tumour staging:

Grade I = Well-differentiated

Grade II = Moderately differentiated

Grade III = Poorly differentiated

Grade IV = Anaplastic

Table 39: Distribution of oral cancer cases according to histopathological differentiation

Histopathological grade	**Categories**	**n**	**%**
Grade I	Well-differentiated	103	60.9
Grade II	Moderately differentiated	58	34.3
Grade III	Poorly differentiated	8	4.7

The oral cancer staging data were documented from the hospital medical record, where only histopathological differentiation data were available. Table 39 showed the distribution of oral cancer patients according to histopathological grading: Majority patients had well-differentiated tumours 103 (60.9%), followed by moderately differentiated tumours 58 (34.3%). Only eight patients had poorly differentiated tumours 4.7%.

4.2.3 Distribution of hospital controls according to admission condition

Table 40 illustrates the disease condition of the controls. As mentioned earlier the study was conducted in a tertiary-level dental hospital. Therefore, the underlying causes of patient admission were mostly dental-related problems. However, care was taken to ensure not recruiting any controls whose disease risk factor is associated with the exposure of interest (Woodward, 2014, p. 227). Based on the WHO ICD ten diseases classification system of controls cause of hospital admission were grouped into three major categories: diseases of the nervous system (G00-G99), diseases of the digestive system (K00-K93), injury, poisoning and certain other consequences of external causes (S00-T98) (WHO, 2014b). As the study site was a dental hospital, majority controls were randomly recruited from the digestive system diseases (K00-K93) 300 (88.76%), followed by injury, poisoning and certain other consequences of external causes (S00-T98) 9.17% and diseases of the nervous system (G00-G99) 2.07%.

Table 40: Underlying causes of controls admission/visit

ICD diagnostic group	**Description of the diseases**	**n**	**%**
Diseases of the nervous system (G00-G99)	Trigeminal neuralgia, Other disorders of trigeminal nerve, Disorder of trigeminal nerve, unspecified, Atypical facial pain, Bell's palsy	7	2.07
Diseases of the digestive system (K00-K93)	Supplementary teeth retained [persistent] primary tooth, Embedded and impacted teeth, Edentulous alveolar ridge, Anomalies of tooth position, Temporomandibular joint disorders, retained dental root, Loss of teeth due to accident or extraction, Exfoliation of teeth due to systemic causes, Disorder of teeth and supporting structures, unspecified	300	88.76
Injury, poisoning and certain other consequences of external causes (S00-T98)	Injuries to the head, Injuries to the neck, Fracture, Injuries to the thorax, Effects of foreign body entering through the natural orifice,	31	9.17
	Total	338	100

4.2.4 Distribution of study subjects according study variables

4.2.4.1 Socio-demographic characteristics

The demographic details of the study participants are presented in Table 41 below. Majority cases were females 52.1% (88), and 47.9% (81) were males. The age of the study participants ranged from 28 to 92 years old, with a mean age of 53.96 ± 12.5 years old. The mean age for female and male participants were 52.59 ± 12.94 and 55.44 ± 11.87 respectively. Most cases 98.2% (166) and controls 97.9% (331) were married. More than half of the cases 58% (98) did not have any formal education, whereas 41.7% (141) controls had formal education. Only 10.1% (48) cases and 9.2% (31) controls completed their primary education. Non-paid work such as house worker was the primary occupation for both female cases 72.7% (64) and controls 79% (139). Small business 30.9% (25), farming 21% (17), and daily labourer 14.8% (12) were the main occupations of male cases. Besides, small business 25.3% (41) and farming 21.6% (35) were also the main profession among male controls. This suggests a suitable representation of study populations.

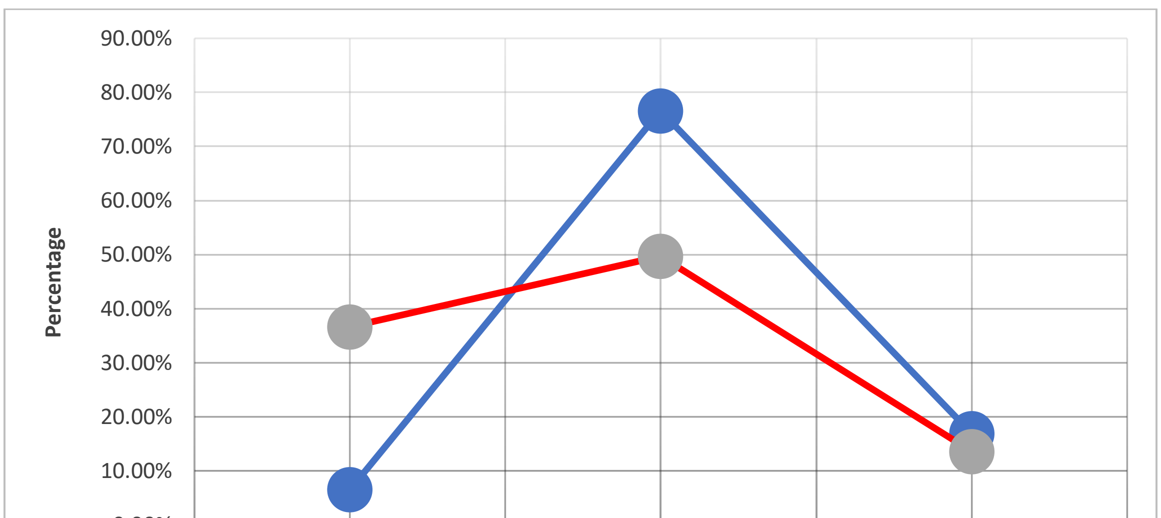
Table 41: Socio-demographic characteristics

Characteristics	Control (%)	Case (%)	Total (%)
Gender			
Male	162 (47.9)	81 (47.9)	243 (47.9)
Female	176 (52.1)	88 (52.1)	264 (52.1)
Marital status			
Single	7 (2.1)	3 (1.8)	10 (2.0)
Married	331 (97.9)	166 (98.2)	497 (98.0)
Age			
<40 years old	41 (12.1)	19 (11.2)	60 (11.8)
40-49 years old	72 (21.3)	32 (18.9)	104 (20.5)
50-59 years old	99 (29.3)	50 (29.6)	149 (29.4)
60-69 years old	81 (24.0)	42 (24.9)	123 (24.3)
>70 years old	45 (13.3)	26 (15.4)	71 (14.0)
Mean age[a]	53.96 ± 12.55	53.97 ± 12.47	53.96 ± 12.51
Education			
No-formal Education	141 (41.7)	98 (58.0)	239 (47.1)
<Primary school completed	53 (15.7)	16 (9.5)	69 (13.6)
Primary school completed	31 (9.2)	17 (10.1)	48 (9.5)
<high school completed	16 (4.7)	14 (8.3)	30 (5.9)
High school completed	62 (18.3)	18 (10.7)	80 (15.8)
College, university	31 (9.2)	6 (3.6)	37 (7.3)
Post-grad degree	4 (1.2)	0	4 (0.8)
Work status			
Govt. employee	14 (4.1)	3 (1.8)	17 (3.4)
Non-Govt employee	27 (8.0)	9 (5.3)	36 (7.1)
Business small	46 (13.6)	28 (16.6)	74 (14.6)
Business large	2 (0.6)	0	2 (0.4)
Farming	35 (10.4)	17 (10.1)	52 (10.3)
Industrial worker	10 (3.0)	7 (4.1)	17 (3.4)
Daily labourer	14 (4.1)	17 (10.1)	31 (6.1)
Other self employed	2 (0.6)	0	2 (0.4)
House worker	141 (41.7)	68 (40.2)	209 (41.2)
Retired	20 (5.9)	9 (5.3)	29 (5.7)
Unemployed, able to work	10 (3.0)	3 (1.8)	13 (2.6)
Unemployed, unable to work	17 (5.0)	8 (4.7)	25 (2.6)

[a] *(Standard deviation)*

4.2.4.2 Distribution of subjects according to height, weight and body mass index

The mean BMI of study participants was 21.96±3.40 Kg/m², ranged from 13.29 – 37.22 kg/m². Overall, males had slightly lower BMI 21.71±3.01 kg/m² compared to females 22.19±3.70 kg/m². Cases mean BMI (20.47 ± 3.79 kg/m²) was slightly lower compared to the controls (22.70 ± 2.92 kg/m²).



	Under weight below 18.5	Normal weight 18.5-24.9	Over weight above 25 and above
Control	6.50%	76.60%	16.90%
Case	36.70%	49.70%	13.60%

Figure 17: BMI across cases and controls

Based on WHO guidelines: (Under-Weight: <18.50; Healthy Weight: 18.50 - 24.99; Over-weight: ≥25.00). Majority cases 84 (49.7%) and controls 255 (76.6%) had a healthy weight. As expected, many cases 62(36.7%) landed in the under-weight category. Whereas, a contrary scenario was detected among controls where many felt into over-weight category 51 (16.90%) (see Figure 17). Table 42 below illustrate the height, weight and BMI categories stratified by case or control status and gender.

Table 42: Distribution of Height, weight and Body Mass Index

Categories	Cases		Controls	
	Male	**Female**	**Male**	**Female**
Height (m)[a]	1.65±0.08	1.50±0.07	1.63±0.07	1.54±0.06
Weight (kg)[a]	54.68±8.7	46.79±8.92	60.06±8.57	54.57±8.21
BMI kg/m²[a]	20.17±3.33	20.73±4.16	22.48±2.52	22.91±3.22
Under-weight (18.5 kg/m²)	31 (38.3%)	31 (35.2%)	11 (6.8%)	11 (6.3%)
Normal weight (18.5-24.9kg/m²)	44 (54.3%)	40 (45.5%)	129 (79.6%)	130 (73.9%)
Over-weight/obese (25 kg/m² and above)	6 (7.4%)	17 (19.3%)	22 (13.6%)	35 (19.9%)

[a] *Mean with Standard deviation*

4.2.4.3 Distribution of subjects according to tobacco smoking

Table 43 represents the distribution of study subjects according to tobacco smoking status. None of the female participants reported smoking. Therefore, distribution of tobacco smoking habits are solely based on male. As predicted, the proportion of smokers and the intensity of smoking were higher among cases. Among cases, 27.8% (47) were tobacco smokers, whereas the corresponding percentage for controls was less (15.4%; 52). Dual use of smoking and SLT was significantly higher among cases (19.5% vs 6.2%).

Regarding the status of cigarette smoking, the ever-smoking status was slightly higher among cases than control (21.3% vs 14.5%). However, the difference was not statistically significant. Type of cigarettes was categorised according to the use of filter and non-filter cigarettes. Among cigarette smokers, most cases (17.2%) and controls (11.8%) used filter cigarettes. Regarding age of onset, cases started smoking cigarettes at younger age than controls (11.8% vs 7.7%). Regarding the frequency of cigarette smoking per day, a higher percentage of cases compared to controls smoked 10 or more cigarettes per day (12.4% vs 6.5%). Concerning the duration of smoking cigarettes, 14.2% (24) of cases smoked for 30 years or less and 7.1% (12) smoked over 30 years. For the controls, the proportions were 8% (27) and 6.5% (22) respectively. The lifetime cumulative exposer of cigarettes smoking did not vary considerably between cases and controls showed that 6.5% (11) of cases and 3.3% (11) of controls had over 20 cigarettes pack-year.

The incidence of ever bidi smoking was considerably greater among cases than controls: 12.4% vs 4.4%. The distribution of the age of onset of bidi smoking showed a higher percentage of cases compared to control started bidi smoking at 18 years old or younger: 5.9% vs 2.1%. The distribution of average intensity of bidi smoking was measured in bidi smoking per day, revealed that more cases than controls smoked over 10 bidi per day and the association was statistically significant (see Table 43). About the total duration of bidi smoking, 5.9% (10) of cases smoked bidi more than 20 years and 6.5% (11) smoked 20 years or less. The proportion was 1.8% (6) and 2.7% (9) for the controls, respectively. Lifetime cumulative exposer (pack-years) of bidi smoking was higher among cases than controls; 5.3% cases had over 10 bidi pack-years and the corresponding percentage for controls was 1.8%.

Fewer number cases and controls have smoked both cigarettes and bidi; 5.3% (9) and 2.4% (8) respectively. Only seven participants ever smoked the water pipe or hukkah, among them 1.8% (3) were cases and 1.2% (4) controls. None of the study subjects ever smoked cigars.

Table 43: Distribution of subjects according to smoking status

Categories	Control (%)	Case (%)	Total (%)	*P-value*
Overall Smoking				**0.001[a]**
Never	286 (84.6)	122 (72.2)	408 (80.5)	
Ever	52 (15.4)	47 (27.8)	99 (19.5)	
Dual use (SLT+smoking)				**<0.001[a]**
None or one	317 (93.8)	136 (80.5)	453 (89.3)	
Using both	21 (6.2)	33 (19.5)	54 (10.7)	
Cigarettes smoking status				
Never	289 (85.5)	133 (78.7)	422 (83.2)	0.06[a]
Ever	49 (14.5)	36 (21.3)	85 (16.8)	
Current	31 (9.2)	23 (13.6)	54 (10.7)	0.15[a]
Only in the past	18 (5.3)	13 (7.7)	31 (6.1)	
Type of Cig smoked				0.15
Never	289 (85.5)	133 (78.7)	422 (83.2)	
Filter	40 (11.8)	29 (17.2)	69 (13.6)	
Non-Filter	9 (2.7)	7 (4.1)	16 (3.2)	
Cig initiation age				
Average**	23.29 (8.86)	22.81 (6.90)	23.08 (8.04)	0.79[b]
Never users	289 (85.5)	133 (78.7)	422 (83.2)	0.15[a]
≤ 20 years old	26 (7.7)	20 (11.8)	46 (9.1)	
>20 years	23 (6.8)	16 (9.5)	39 (7.7)	
Cig per day				0.06[b]
Average**	8.86 (5.19)	11.47 (7.49)	9.96 (6.36)	*continued*
Cig per day				0.06
Never users	289 (85.5)	133 (78.7)	422 (83.2)	
< 10 per day	27 (8.0)	15 (8.9)	42 (8.3)	
≥ 10 per day	22 (6.5)	21 (12.4)	43 (8.5)	

Categories	Control (%)	Case (%)	Total (%)	*P-value*
Total years of cig smoking				
Average**	28.33 (12.23)	24.72 (12.94)	26.80 (12.59)	0.19[b]
Never users	289 (85.5)	133 (78.7)	422 (83.2)	0.08[a]
≤30 years	27 (8.0)	24 (14.2)	51 (10.1)	
>30 years	22 (6.5)	12 (7.1)	34 (6.7)	
Cig Pack-years				
Average **	13.53 (10.03)	14.87 (12.29)	14.10 (10.99)	0.07[b]
Never users	289 (85.5)	133 (78.7)	422 (83.2)	0.10[a]
0-20 pack-years	38(11.2)	25 (14.8)	63 (12.4)	
>20 pack-years	11(3.3)	11 (6.5)	22 (4.3)	
Bidi smoking status				**0.001[a]**
Never	323 (95.6)	148 (87.6)	471 (92.6)	
Ever	15 (4.4)	21 (12.4)	36 (7.1)	
Age of bidi onset				
Average age**	19.73 (6.71)	21.81 (7.88)	20.94 (7.39)	0.41[b]
Never smoked	323 (95.6)	148 (87.6)	471 (92.9)	**0.004[a]**
≤18 years old	7 (2.1)	10 (5.9)	17 (3.4)	
> 18 years old	8 (2.4)	11 (6.5)	19 (3.7)	
Number of bidis per day				
Average bidi per day**	8.53 (4.20)	12.10 (7.70)	10.61 (6.64)	0.08[b]
Number of bidis per day				
Never smoked	323 (95.6)	148 (87.6)	471 (92.9)	**0.005[a]**
1-5 bidi per day	4 (1.2)	3 (1.8)	7 (1.4)	
6-10 bidi per day	9 (2.7)	12 (7.1)	21 (4.1)	
>10 bidi per day	2 (0.5)	6 (3.6)	8 (1.6)	
Total years of bidi smoking				
Average years of use**	21.67 (14.42)	22.10 (13.40)	21.92 (13.63)	0.93[b]
Never smoked	323 (95.6)	148 (87.6)	471 (92.9)	**0.004[a]**
≤20 years	9 (2.7)	11 (6.5)	20 (3.9)	
>20 years	6 (1.8)	10 (5.9)	16 (3.2)	

Categories	Control (%)	Case (%)	Total (%)	*P-value*
Bidi Pack-year				
Average	8.2 (6.45)	11.14 (11.23)	9.92 (9.54)	0.37[b]
Never smoked	323 (95.6)	148 (87.6)	471 (92.9)	**0.004[a]**
≤10 pack-year	9 (2.7)	12 (7.1)	21 (4.1)	
>10 pack-year	6 (1.8)	9 (5.3)	15 (3.0)	
Dual use of Cig and bidi				0.08[a]
Never or one	330 (97.6)	160 (94.7)	490 (96.6)	
Dual use	8 (2.4)	9 (5.3)	17 (3.4)	
Waterpipe/Hukkah				0.65[a]
Never smoked	334 (98.8)	166 (98.2)	500 (98.6)	
Ever Smoked	4 (1.2)	3 (1.8)	7 (1.4)	

*** Mean (Standard deviation)*
[a] *Chi-square/ fisher-exact test*
[b] *t-test*

4.2.4.4 Distribution of subjects accordingly oral health indicators

The distribution of subjects according to oral health indicators is presented in Table 44. The proportion of individuals wearing a partial denture did not vary significantly between cases and controls. Only 12.4% (21) cases and 13% (44) controls wore partial dentures. Among cases using fingers was the most common method of cleaning teeth 65.7% (111) and toothbrush 49.1% (166) among controls. However, 39.1% (132) of the controls also used fingers to clean their teeth. Regarding the substance used to clean teeth, 32.5% (55) cases did not use any cleaning substance and 43.2% (73) used toothpowder. The proportions for controls were 15.7% (53) and 37% (125) respectively. Concerning the gum bleeding and mouth ulcer status, the distribution of subjects did not differ markedly between cases and controls. However, controls were more watchful about oral health and visited dentists more often (66.9% vs 55.0%).

Table 44: Distribution of subjects according to oral health indicators

Categories	Control (%)	Case (%)	Total (%)	*P-value*
Partial Denture use				0.85[a]
No	294 (87.0)	148 (87.6)	442 (87.2)	
Yes	44 (13.0)	21 (12.4)	65 (12.8)	
Instrument use				**<0.001[b]**
Toothbrush	166 (49.1)	39 (23.1)	205 (40.4)	
Fingers	132 (39.1)	111 (65.7)	243 (47.9)	
Sticks	40 (11.8)	19 (11.2)	59 (11.6)	
Frequency of cleaning				**0.002[a]**
Once a day or less	202 (59.8)	125 (74.0)	327 (64.5)	
Twice a day or more	136 (40.2)	44 (26.0)	180 (35.5)	
Substance used to clean				**<0.001[b]**
Toothpaste	160 (47.3)	41 (24.3)	201 (39.6)	
Toothpowder	125 (37.0)	73 (43.2)	198 (39.1)	
None or others	53 (15.7)	55 (32.5)	108 (21.3)	
Status of gum bleeding				0.62[a]
No	241 (71.3)	117 (69.2)	358 (70.6)	
Yes	97 (28.7)	52 (30.8)	149 (29.4)	
History of mouth ulcer				0.61[a]
No	327 (96.7)	162 (95.9)	489 (96.4)	
Yes	11 (3.3)	7 (4.1)	18 (3.6)	
Frequency of dental visit				**0.009[a]**
No	112 (33.1)	76 (45.0)	188 (37.1)	
Yes	226 (66.9)	93 (55.0)	319 (62.9)	

[a] *Chi-square test;* [b] *Fisher-exact test*

4.2.4.5 Distribution of other risk factors

Table 45 shows the distribution of subjects according to alcohol drinking and family history of cancer. Overall, very few study subjects ever drank alcohol, 3% (5) cases and 0.90% (3) controls ever drank alcohol. Drinking socially was a major occasion. Regarding the types of alcoholic beverages, only two types of alcohol was consumed: local toddy and hard liquor.

Same as alcohol, very few study subjects had first-degree relatives with a cancer history. The history of cancer among relatives did not differ substantially between cases and controls. Only 2.7% (9) controls and 1.8% (3) cases reported having first-degree relatives who had cancer.

Table 45: Distribution of subjects according to other risk factors

Categories	Control (%)	Case (%)	Total (%)
Alcohol drinking habit			
Never	335 (99.1)	164 (97.0)	449 (98.4)
Current	1 (0.30)	2 (1.2)	3 (0.6)
Only in the past	2 (0.60)	3 (1.8)	5 (1)
Time of drinking alcohol			
Between meals	0	2 (40.0)	2 (25)
Only at social events	3 (100)	3 (60.0)	6 (75)
Type of alcohol drink			
Local toddy	1 (33.3)	3 (60.0)	4 (50)
Hard liquor	2 (66.7)	2 (40.0)	4 (50)
Family history of cancer			
None	329 (97.3)	166 (98.2)	495 (97.6)
Yes	9 (2.7)	3 (1.8)	12 (2.4)
Type of cancer			
Neck cancer	0	1 (33.3)	1 (9.1)
Liver cancer	2 (25.0)	1 (33.3)	3 (27.3)
Lung cancer	0	1 (33.3)	1 (9.1)
Leukaemia	1 (12.5)	0	1 (9.1)
Breast cancer	1 (12.5)	0	1 (9.1)
Ovarian cancer	1 (12.5)	0	1 (9.1)
Oral cancer	1 (12.5)	0	1 (9.1)
Oesophageal cancer	1 (12.5)	0	1 (9.1)
Prostate cancer	1 (12.5)	0	1 (9.1)

4.2.5 Odds ratios for oral cancer according to study variables

4.2.5.1 Odds ratios for socio-demographic variables

Table 46 shows the odds ratios for oral cancer association with socio-demographic variables (education and work status).

There was an elevated risk of oral cancer among subjects who did not have any formal education. The adjusted odds ratio was 1.98 (95%CI: 1.34-2.94) and significantly associated with oral cancer risk (p=0.001). However, the variable lost its significance when further adjusted for SLT use status, smoking status, and oral hygiene factors. Although elevated risk was observed for paid workers compared to unemployed or unpaid workers, but it was not statistically significant.

Table 46: Odds ratio for oral cancer of demographic variables

Categories	Controls	Cases	Crude OR (95%CI) [a]	Adjusted OR (95% CI) [b]	Fully adjusted OR (95% CI) [c]	*P-value*[d]
Education status						
Formal education	141	98	Reference	Reference	Reference	0.76
No-formal education	197	71	1.93 (1.33-2.80)	1.98 (1.34-2.94)	1.07 (0.67 -1.74)	
Work status						
Unemployed or unpaid	188	88	Reference	Reference	Reference	0.38
Paid work	150	81	1.15 (0.80-1.67)	1.36 (0.82-2.26)	1.31 (0.72-2.42)	

Abbreviations: CI, confidence interval; N, number; OR, odds ratio

a Crude OR: OR and 95% CI were calculated using unconditional logistic regression

[b] OR and 95% CI were calculated using unconditional logistic regression, adjusted for, age, gender (matching factors)

[c] OR and 95% CI were calculated using unconditional logistic regression, adjusted for, age, gender, education status, employment status and SLT use status and smoking status, and oral health indicators

[d] P-values for fully adjusted model

4.2.5.2 Tobacco smoking (among males)

The risk of oral cancer increased with tobacco smoking. Table 47 shows the odds ratios for oral cancer from different forms of smoking. The findings revealed that ever smokers were nearly three times more likely to have oral cancer compared to never smokers: [ORadj = 2.66 (95%CI: 1.41-5.02)] and remained significant after adjustment.

Regarding the type of smoking, ever smoking cigarettes was associated with nearly two-fold increased risk of oral cancer when the comparative group was never smokers. The association was significant in the crude model and the model adjusted for age. However, when the model was further adjusted for work, education status, SLT use status and BMI, it missed the significance, [ORadj = 1.69 (95%CI: 0.90-3.20), p=0.10]. Among the type of cigarettes, non-filter cigarettes smoking was associated with an increased risk of oral cancer, OR= 1.95 (95%CI: 0.69-5.56) and the association was statistically significant, p=0.04. However, after adjusting for other covariates, the association was not statistically significant p =0.09. No clear trend was observed for cigarette initiation age. Regarding the intensity of cigarette smoking, the average number of cigarettes smoked per day was dichotomised as, <10 per day and ≥10 per day. Smoking ten or more cigarettes per day was associated with two folds increased risk of oral cancer, OR=2.40 (95%CI: 1.20-4.78), however the association was not statistically significant. Also, the cumulative exposure to cigarette smoking (pack-year) was not statistically significant.

A significant risk of oral cancer was associated with ever bidi smoking, OR_{adj}=2.46 (95%CI: 1.08-5.60). Smoking bidi at a younger age elevated the oral cancer risk, starting smoking bidi at the age of 18 or lower had a higher risk of developing oral cancer compared to non-smokers and the adjusted ORadj=2.84 (95%CI: 0.93-8.65). The liner trend was significant in the final adjusted model, p=0.03. However, when entered as a categorical variable into the final adjusted model, the likelihood ratio test lost the statistical significance (p=0.09). After the average number of bidis smoked per day was trichotomised as 1-5, 6-10 and 10+ bidi, increased smoking yielded higher risk of oral cancer. The test of linear trend was statistically significant in the final adjusted model, p=0.008. However, when the variable was entered as a categorical variable, the association just missed its statistical significance p=0.07. Regarding the lifetime exposure, the liner trend for bidi smoking pack-years was significant in crude model and matching factors (age and gender) adjusted model. However, lost its significance in fully adjusted model.

Table 47: Odds Ratio with 95% confidence interval for oral cancer associated with smoking

Categories	Control	Case	Crude OR (95% CI) [a]	Adjusted OR (95% CI) [b]	Fully adjusted OR (95%CI) [c]	*P-value* [d]
Overall smoking						**0.002**
Never	110	34	Reference	Reference	Reference	
Ever users	52	47	2.92 (1.69-5.07)	2.91 (1.67-5.06)	2.66 (1.41-5.02)	
Cig smoking status						0.10
Never	113	45	Reference	Reference	Reference	
Ever	49	36	1.84 (1.06-3.20)	1.84 (1.06-3.20)	1.69 (0.90-3.20)	
Type of Cig smoked						0.22
Never	113	45	Reference	Reference	Reference	
Filter	40	29	1.82 (1.01-3.28)	1.83 (1.02-3.31)	1.82 (0.93-3.59)	
Non-Filter	9	7	1.95 (0.69-5.56)	1.86 (0.65-5.37)	1.19 (0.32-4.35)	
Cig initiation age						0.83
Never users	113	45	Reference	Reference	Reference	
≤ 20 years old	26	20	1.93 (0.98-3.80)	1.94 (0.98-3.82)	1.96 (0.90-4.25)	
>20 years	23	16	1.75 (0.85-3.61)	1.73 (0.83-3.57)	1.41 (0.59-3.33)	
P-for trend [e]			0.06	0.06	0.27	
Cig per day						0.25
Never users	113	45	Reference	Reference	Reference	
< 10 per day	27	15	1.39 (0.68-2.86)	1.39 (0.68-2.86)	1.53 (0.66-3.55)	
≥ 10 per day	22	21	2.40 (1.20-4.78)	2.38 (1.19-4.76)	1.85 (0.84-4.06)	
P-for trend [e]			0.07	0.07	0.43	*continued*
Cig Pack-years						0.24
Never users	113	45	Reference	Reference	Reference	
0-20 pack-years	38	25	1.65 (0.90-3.04)	1.66 (0.90-3.05)	1.58 (0.78-3.21)	
>20 pack-years	11	11	2.51 (1.02-6.20)	2.47 (1.00-6.11)	2.02 (0.73-5.61)	
P-for trend			0.05	0.06	0.22	

Categories	Control	Case	Crude OR (95% CI) [a]	Adjusted OR (95% CI) [b]	Fully adjusted OR (95%CI) [c]	*P-value*[d]
Bidi smoking status						***0.03***
Never	147	60	Reference	Reference	Reference	
Ever	15	21	3.43 (1.66-7.10)	3.46 (1.64-7.29)	2.46 (1.08-5.60)	
Age of bidi onset						0.09
Never smoked	147	60	Reference	Reference	Reference	
≤18 years old	7	10	3.50 (1.27-9.62)	3.53 (1.26-9.89)	2.84 (0.93-8.65)	
> 18 years old	8	11	3.37 (1.29-8.79)	3.39 (1.29-8.95)	2.16 (0.74-6.30)	
P-for trend			***0.001***	***0.001***	***0.03***	
Number of bidis per day						0.07
Never smoked	147	60	Reference	Reference	Reference	
1-5 bidi per day	4	3	1.84 (0.40-8.46)	1.85 (0.40-8.56)	1.23 (0.23-6.61)	
6-10 bidi per day	9	12	3.27 (1.31-8.16)	3.30 (1.30-8.39)	1.99 (0.71-5.59)	
>10 bidi per day	2	6	7.35 (1.44-37.45)	7.41 (1.44-38.01)	8.50 (1.43-50.39)	
P-for trend			***0.001***	***0.001***	***0.008***	
Bidi Pack-year						0.10
Never smoked	147	60	Reference	Reference	Reference	
≤10 pack-year	9	12	3.27 (1.31-8.56)	3.29 (1.30-8.33)	2.57 (0.93-7.09)	
>10 pack-year	6	9	3.67 (1.25-10.78)	3.71 (1.24-11.03)	2.31 (0.70-7.58)	
P-for trend			**0.008**	**0.009**	0.08	

Abbreviations: CI, confidence interval; N, number; OR, odds ratio.; SLT, Smokeless tobacco, Cig, Cigarettes
a Crude OR: OR and 95% CI were calculated using unconditional logistic regression
b OR and 95% CI were calculated using unconditional logistic regression, adjusted for age (cat)
c OR and 95% CI were calculated using unconditional logistic regression, adjusted for, age (cat), education status (formal education/no-formal education), employment status (Cat), SLT use status (never/ever) and BMI (Continuous variable)
d P-values for fully adjusted model
[e] p-for the linear trend was derived from including the variable as a continuous variable in the regression model

4.2.5.3 Oral health indicators

Table 48 shows the association between oral health indicators and the risk of oral cancer. No association was observed between the status of the partial dentures and the risk of oral cancer. There were only two patients with the complete denture, therefore, had to drop from the analysis. Oral hygiene habits such as the instrument used to clean teeth, the frequency of teeth cleaning was associated with significant risk after adjusting for other measures. Patients who used fingers to clean their teeth were nearly two times more likely to develop oral cancer compared to who uses the toothbrush, ORadj = 1.95 (95%CI: 1.15-3.29). Cleaning teeth twice or more in a day proved to be protective against oral cancer, the odds ratio for patients who cleaned their teeth twice or more per day was ORadj= 0.32 (95%CI: 0.20-0.51) when the relative group cleaned teeth once or less per day. Subjects who did not use any substances- or used other substances rather than toothpaste or toothpowder- were four times more likely to develop oral cancer, OR = 4.05 (95%CI: 2.43-6.74). However, after adjustment for other measures, the risk reduced by nearly half and just missed the statistical significance ($p=0.05$). The status of gum bleeding and history of mouth ulcer showed no association. However, visiting dentists regularly reduced the risk of oral cancer significantly ($p<0.01$). Though after adjustment the variable lost its significance.

The effect of oral health risk factors dependent upon SLT use status was assessed in Table 49. The analysis showed poor oral hygiene practice was a significant risk factors for oral cancer only among ever SLT users: the instrument used for cleaning teeth and frequency of cleaning teeth per day had significantly increased oral cancer risk. The odds ratio for ever chewers who used fingers to clean their teeth was, ORadj = 2.29 (95%CI: 1.18-4.43) and ORadj = 1.69 (95%CI: 0.69-4.12) for those used sticks when the relative group was toothbrush users. Increased frequency of cleaning teeth per day reduced the risk of oral cancer among ever chewers. Ever chewers who cleaned their teeth twice or more per day were, ORadj= 0.22 (95%CI: 0.13-0.38) times less likely to have oral cancer compared to those clean their teeth once or less per day. Though there was an increasing trend of risk associated with substance use among ever chewers, but it was not statistically significant. Among never chewers regular visits to the dentist was only significant variable. The odds ratio for never chewers who regularly visited was, ORadj = 0.43 (95%CI: 0.19-0.97) when the relative group was who never visited the dentist.

Table 48: Odds ratio with 95% confidence interval for oral health indicators and oral cancer risk

Categories	Control	Case	Crude OR (95% CI) [a]	Adjusted OR (95% CI) [b]	Fully adjusted OR (95% CI) [c]	*P-value*[d]
Partial Denture use						0.78
No	294	148	Reference	Reference	Reference	
Yes	44	21	0.94 (0.54-1.65)	0.93 (0.53-1.62)	0.92 (0.49-1.70)	
Instrument use for cleaning teeth						
Toothbrush	166	39	Reference	Reference	Reference	**0.03**
Fingers	132	111	3.58 (2.32-5.50)	3.93 (2.49-6.20)	1.95 (1.15-3.29)	
Sticks	40	19	2.02 (1.06-3.86)	2.10 (1.12 -4.18)	1.23 (0.59-2.55)	
Frequency of cleaning teeth						**<0.001**
Once a day or less	202	125	Reference	Reference	Reference	
Twice a day or more	136	44	0.52 (0.34-0.78)	0.51 (0.34-0.77)	0.32 (0.20-0.51)	
Substance used to clean teeth						
Toothpaste	160	41	Reference	Reference	Reference	0.05
Toothpowder	125	73	2.28 (1.45-3.57)	2.43 (1.52-3.87)	1.47 (0.87-2.48)	
None or others	53	55	4.05 (2.43-6.74)	4.37 (2.56-7.43)	2.10 (1.15-3.86)	
Status of gum bleeding						0.07
No	241	117	Reference	Reference	Reference	
Yes	97	52	1.10 (0.73-1.65)	1.11 (0.74-1.66)	1.09 (0.69-1.73)	
History of mouth ulcer						0.83
No	327	162	Reference	Reference	Reference	
Yes	11	7	1.28 (0.49-3.37)	1.26 (0.48-3.31)	0.89 (0.31-2.54)	
Frequency of dental visit						0.06
No	112	76	Reference	Reference	Reference	*continued*
Yes	226	93	0.60 (0.41-0.88)	0.61 (0.42-0.89)	0.66 (0.43-1.01)	

Abbreviations: CI, confidence interval; N, number; OR, odds ratio
a Crude OR: OR and 95% CI were calculated using unconditional logistic regression
b OR and 95% CI were calculated using unconditional logistic regression, adjusted for, age (cat), gender (cat)
[c] OR and 95% CI were calculated using unconditional logistic regression, adjusted for, age (cat), gender (cat), education status (cat), employment status (cat), SLT use status (cat) and smoking status (cat)
d P-values for fully adjusted model

Table 49: Odds ratio with 95% confidence interval for oral cancer risk associated with oral health indicators stratified by SLT use status

Characteristics	Ever SLT users			Never SLT user		
	Cont. (%)	Case (%)	Adjusted OR (95%CI) a	Cont. (%)	Case (%)	Adjusted OR (95%CI) a
Partial Denture use						
No	105 (84.0)	123 (88.5)	Reference	189 (88.7)	25 (83.3)	Reference
Yes	20 (16.0)	16 (11.5)	0.77 (0.37-1.60)	24 (11.3)	5 (16.7)	1.33 (0.43-4.13)
***P-value*[b]**			*0.49*			*0.62*
Instr. use for cleaning						
Toothbrush	33 (26.4)	23 (16.5)	Reference	133 (62.4)	16 (53.3)	Reference
Fingers	75 (60.0)	99 (71.2)	2.29 (1.18-4.43)	57 (26.8)	12 (40.0)	1.68 (0.65-4.29)
Sticks	17 (13.6)	17 (12.2)	1.69 (0.69-4.12)	23 (10.8)	2 (6.7)	0.53 (0.10-2.69)
***P -value*[b]**			***0.04***			*0.33*
Freq. of cleaning						
Once a day or less	48 (38.4)	102(73.4)	Reference	154 (72.3)	23 (76.7)	Reference
Twice a day or more	77 (61.6)	37 (26.6)	0.22 (0.13-0.38)	59 (27.7)	7 (23.3)	0.74 (0.29-1.92)
***P -value*[b]**			***<0.001***			*0.54*
Subs. used to clean						
Toothpaste	38 (30.4)	27 (19.4)	Reference	122 (57.3)	14 (46.7)	Reference
Toothpowder	55 (44.0)	64 (46.0)	1.81 (0.94-3.49)	70 (32.9)	9 (30.0)	0.93 (0.35-2.46)
None or others	32 (25.6)	48 (34.5)	2.37 (1.13-4.93)	21 (9.9)	7 (23.3)	2.99 (0.90-9.89)
***P -value*[b]**			*0.06*			*0.14* *(Continued)*

Characteristics	Ever SLT users			Never SLT user		
	Cont. (%)	Case (%)	Fully adjusted OR (95%CI) [a]	Cont. (%)	Case (%)	Fully adjusted OR (95%CI) [a]
Status of gum bleeding						
No	88 (70.4)	100 (71.9)	Reference	153 (71.8)	17 (56.7)	Reference
Yes	37 (29.6)	39 (28.1)	0.89 (0.51-1.54)	60 (28.2)	13 (43.3)	1.54 (0.67-3.53)
P-value [b]			*0.67*			*0.30*
History of mouth ulcer						
No	118 (94.4)	133 (95.7)	Reference	209 (98.1)	29 (96.7)	Reference
Yes	7 (5.6)	6 (4.3)	0.78 (0.25-2.45)	4 (1.9)	1 (3.3)	1.06 (0.09-12.52)
P-value [b]			*0.68*			*0.96*
Freq. of dental visit						
No	45 (36.0)	60 (43.2)	Reference	67 (31.5)	16 (53.3)	Reference
Yes	80 (64.0)	79 (56.8)	0.80 (0.48-1.33)	146 (68.5)	14 (46.7)	0.43 (0.19-0.97)
P-value [b]			*0.38*			***0.04***

Abbreviations: CI, confidence interval; N, number; OR, odds ratio.; SLT, Smokeless Tobacco

a OR and 95% CI were calculated using unconditional logistic regression, adjusted for, age, gender, education status, employment status and smoking status

[b] p-value for fully adjusted model

4.2.5.4 Body Mass Index and Oral cancer

Table 50 shows the association between BMI at diagnosis and oral cancer. Present case-control study findings showed that leanness is associated with increased risk of oral cancer after adjustment for other covariates. Compared to normal weight (18.50 -24.99kg/m²), under-weight (<18.5 kg/m²), increased oral cancer risk by seven folds, ORadj = 7.07 (95%CI: 3.85-13.01). The linear trend for the association was significant and did not lost its significance after adjustment for other measures ($p<0.001$). After examining across SLT use status the association remained significant for both ever and never SLT users and the linear trend was significant. Although imprecise, inverse association for subjects with BMI≥25kg/m² was present only in SLT users (see Table 51).

Table 50: Odds ratio with 95% Confidence interval for oral cancer of Body Mass Index

Categories	Controls	Cases	Crude OR (95%CI) [a]	Adjusted OR (95% CI) [b]	Fully adjusted OR (95% CI) [c]	*P- value*
BMI (kg/m²)						
Normal-weight 18.50 - 24.99	259	84	Reference	Reference	Reference	***<0.001***
Under-weight <18.50	22	62	8.69 (5.04-14.99)	8.67 (5.02-14.97)	7.07 (3.85-13.01)	
Over-weight ≥ 25	57	23	1.24 (0.72-2.14)	1.24 (0.72-2.14)	1.11 (0.60-2.03)	
P-for trend[d]			***<0.001***	***<0.001***	***<0.001***	

Abbreviations: CI, confidence interval; N, number; OR, odds ratio

a Crude OR: OR and 95% CI were calculated using unconditional logistic regression.

[b] OR and 95% CI were calculated using unconditional logistic regression, adjusted for age, gender (matching factors)

[c] OR and 95% CI were calculated using unconditional logistic regression, adjusted for, age, gender, education status, employment status and SLT use status and smoking status

[d] *p-for the linear trend was derived from including the variable as a continuous variable in the regression model*

Table 51: Odds ratio with 95% Confidence Interval for oral cancer of body mass index in ever and never smokeless tobacco users

Characteristics	**Ever SLT users**			**Never SLT users**		
	Cont. (%)	**Case (%)**	**Fully adjusted OR (95%CI) [b]**	**Cont. (%)**	**Case (%)**	**Fully adjusted OR (95%CI) [b]**
BMI (kg/m²)						
Normal weight18.50 - 24.99	91 (72.8)	68 (48.9)	Reference	168 (78.9)	16 (53.3)	Reference
Under-weight <18.50	10 (8.0)	52 (37.4)	6.81 (3.19-14.56)	12 (5.6)	10 (33.3)	8.37 (2.71-25.80)
Over-weight ≥ 25	24 (19.2)	19 (13.7)	0.95 (0.47-1.93)	33 (15.5)	4 (13.4)	1.64 (0.48-5.60)
P-for trend[c]			***<0.001***			***0.001***

Abbreviations: CI, confidence interval; N, number; OR, odds ratio

a Crude OR: OR and 95% CI were calculated using unconditional logistic regression

[b] OR and 95% CI were calculated using unconditional logistic regression, adjusted for, age, gender (matching factors), education status, employment status, smoking status

[c] *p-for the linear trend was derived from including the variable as a continuous variable in the regression model*

4.2.6 Association between smokeless tobacco use and oral cancer risk

4.2.6.1 Distribution of subjects according to smokeless tobacco use status

Frequency distribution of SLT use habits is presented in Table 52. The overall chewing habit was substantially higher among cases than controls (82.2% vs 37.0%). The chewing habits with SLT was much higher among cases compare to control, 80.1% vs 32.8%. SLT use was more prevalent among female compared to male cases, where 87.2% (68) female compared to 72.6% (53) male cases were ever SLT users.

Regarding the type of SLT use, BQ with Zarda was the most popular form of SLT, 39.6% (201) among all study subjects. However, BQ with Sadapata was predominantly used by the female cases (see Table 53).

About the age of onset, cases started using SLT earlier than the controls, the mean age of SLT initiation among cases was 22.78±7.57 vs 23.35±9.5 among controls. When stratified across different age groups, majority cases and controls 49.0% vs 18.3% started using SLT at the age of 20 or below. A similar trend was observed across different genders (see Table 53). However, a higher percentage of women cases started using SLT at a younger age compared to men (59.0% vs 38.4%).

About frequency of SLT use, on average cases had consumed SLT more frequently than controls (8.78±4.79 vs 6.33±5.09). The highest frequency was observed among female cases 9.32±5.19 (see Table 53). Further, frequency of SLT dichotomised into two groups, a substantial difference was observed among cases and controls, showed that 57.0% of cases than controls 12.3% used SLT more than five times a day.

Regarding the duration of holding SLT in the mouth, a substantial difference was observed between cases and controls. The analysis showed that 26.5% cases compared to 5.4% controls held the SLT in their mouth for more than 10 minutes. On average, cases held the SLT in their mouth longer than controls (13.98±13.67 vs 10.30±8.07) and the association was statistically significant (see Table 53).

Regarding the duration of SLT use, the average years of SLT use was almost similar among cases and controls (30.35±13.08 vs 31.34±14.84). Additionally, when total years of use was trichotomized, 39.7% of cases and 17.7% of controls used SLT for more than 30 years. Among genders, 43.6% of women cases and 35.6% of men cases used SLT for more than 30 years (see Table 53). The intensity of SLT use was measured using lifetime cumulative exposure to SLT, in chew-years. The analysis showed a high proportion of cases compared to controls were in more than 40-chew-years category (19.3% vs 3.5%). The highest average chew-years were reported among female cases, 30.53±22.87. More than 24% of female cases corresponding to 13% male cases were in more than 40 chew-years category (see Table 53).

Table 52: Distribution of subjects according to smokeless tobacco use indicators

Categories	Cases (%)	Controls (%)	Total (%)	*P-value*
Chewing habits[d]				
Never	30 (17.8)	213 (63.0)	243 (47.9)	**<0.001**[a]
Ever chewers	139 (82.2)	125 (37.0)	264 (52.1)	
Current chewers	115 (68.0)	89 (26.3)	204 (40.2)	**<0.001**[a]
Past chewers	24 (14.2)	36 (10.7)	60 (11.8)	
Chewing habits with SLT [e]				
Never	30 (19.9)	213 (67.2)	243 (51.9)	**<0.001**[a]
Ever chewres	121 (80.1)	104 (32.8)	225 (48.1)	
Chewing habit without SLT [f]				
Never	30 (62.5)	213 (91.0)	243 (86.2)	**<0.001**[a]
Ever chewers	18 (37.5)	21 (9.0)	39 (13.8)	
Type of chewing products				**<0.001**[a]
None	30 (17.8)	213 (63.0)	243 (47.9)	
BQ with Zarda	105 (62.1)	96 (28.4)	201 (39.6)	
BQ without Zarda	18 (10.7)	21 (6.2)	39 (7.7)	
BQ with sadapata	11 (6.5)	3 (0.9)	14 (2.8)	
Gul/Panmasala	5 (3.0)	5 (1.5)	10 (2.0)	
Age at SLT initiation				
Mean age[c]	22.78±7.57	23.35±9.5	23.04±8.51	0.61[b]
Never users	30 (19.9)	213 (67.2)	243 (51.9)	**<0.001**[a]
≤20 years old	74 (49.0)	58 (18.3)	132 (28.2)	
21-30 years old	31 (20.5)	30 (9.5)	61 (13.0)	
>30 years old	16 (10.6)	16 (5.0)	32(6.8)	

Categories	Cases (%)	Controls (%)	Total (%)	*P-value*
SLT use frequency				
Average per day[c]	8.78±4.79	6.33±5.09	7.65±5.07	**<0.001[b]**
Never users	30 (19.9)	213 (67.2)	243 (51.9)	**<0.001[a]**
1-5 per day	35 (23.2)	65 (20.5)	100 (21.4)	
>5 per day	86 (57.0)	39(12.3)	125 (26.7)	
SLT holding duration				
Avg minutes of holding[c]	13.98±13.67	10.30±8.07	12.27±11.54	**0.01[b]**
Never users	30 (19.9)	213 (67.2)	243 (51.9)	**<0.001[a]**
≤10 minutes	81 (53.6)	87 (27.4)	168 (35.9)	
>10 minutes	40 (26.5)	17 (5.4)	57 (12.2)	
Total Years of SLT use				
Avg. years of use[c]	30.35±13.08	31.34±14.84	30.81±13.90	0.59[b]
Never users	30 (19.9)	213 (67.2)	243 (51.9)	**<0.001[a]**
≤30 years	61 (40.4)	48 (15.1)	109 (23.3)	
>30 years	60 (39.7)	56 (17.7)	116 (24.8)	
Lifetime exposure to SLT				
Average Chew-years[c]	28.11±21.89	20.92±22.67	24.79±22.49	**0.02[b]**
Never user	30 (20.0)	213 (67.2)	243 (52.0)	**<0.001[a]**
≤20 chew-years	54 (36.0)	65 (20.5)	119 (25.5)	
21-40 chew-years	37 (24.7)	28 (8.8)	65 (13.9)	
>40 chew-years	29 (19.3)	11 (3.5)	40 (8.6)	

Abbreviations: BQ (Betel Quid).; SLT, Smokeless Tobacco.

[a] *p-value derived from chi-square test/Fisher-exact test*

[b] *p-value derived from t-test.*

[c] *Mean with Standard Deviation*

[d] *Chewing habits- Overall chewing habits both with and without SLT*

[e] *Chewing habit with tobacco- such as BQ with Zarda or sadapata, Gul, Panmasala containing tobacco, arecanut with tobacco, sadapata alone.*

[f]*Chewing habit without tobacco- such as BQ without tobacco, areca nut alone, panmasala without tobacco.*

Table 53: Distribution of smokeless tobacco use by gender among cases and controls

Categories	Male			Female		
	Control (%)	Case (%)	*P-value*	Control (%)	Case (%)	*P-value*
Chewing habits[d]						
Never	103 (63.6)	20 (24.7)	**<0.001[a]**	110 (62.5)	10 (11.4)	**<0.001[a]**
Ever chewers	59 (36.4)	61 (75.3)		66 (37.5)	78 (88.6)	
Current chewers	45 (27.8)	48 (59.3)	**<0.001[a]**	44 (25.0)	67 (76.1)	**<0.001[a]**
Past chewres	14 (8.6)	13 (16.0)		22 (12.5)	11 (12.5)	
Chewing habit with SLT[e]						
Never	103 (67.3)	20 (27.4)	**<0.001[a]**	110 (67.1)	10 (12.8)	**<0.001[a]**
Ever chewers	50 (32.7)	53 (72.6)		54 (32.9)	68 (87.2)	
Chewing habit without SLT[f]						
Never	103 (92.0)	20 (71.4)	**<0.007[a]**	110 (90.2)	10 (50.0)	
Ever chewers	9 (8.0)	8 (28.6)		12 (9.8)	10 (50.0)	
Type of chewing products			**<0.001[a]**			
None	103 (63.6)	20 (24.7)		110 (62.5)	10 (11.4)	**<0.001[a]**
BQ with Zarda	46 (28.4)	48 (59.3)		50 (28.4)	57 (64.8)	
BQ without Zarda	9 (5.6)	8 (9.9)		12 (6.8)	10 (11.4)	
BQ with sadapata	2 (1.2)	3 (3.7)		1 (0.6)	8 (9.0)	
Gul/Panmasala	2 (1.2)	2 (2.5)		3 (1.7)	3 (3.4)	
Age at SLT initiation						
Mean age [c]	24.36±10.49	24.30±8.56	0.98[b]	22.43±8.50	21.59±6.52	0.54[b]
Never users	103 (67.3)	20 (27.4)	**<0.001[a]**	110 (67.1)	10 (12.8)	**<0.001[a]**
≤20 years old	26 (17.0)	28 (38.4)		32 (19.5)	46 (59.0)	

Categories	Male			Female		
	Control (%)	Case (%)	*p-value*	Control (%)	Case (%)	*p-value*
21-30 years old	17 (11.1)	16 (21.9)		13 (7.9)	15 (19.2)	
>30 years old	7 (4.6)	9 (12.3)		9 (5.5)	7 (9.0)	
Freq of SLT use						
Average per day[c]	6.60±4.62	8.08±4.17	0.09[b]	6.09±5.50	9.32±5.19	**0.001[b]**
Never users	103 (67.3)	20 (24.7)	**<0.001[a]**	110 (67.1)	10 (12.8)	**<0.001[a]**
1-5 per day	29 (19.0)	19 (26.0)		36 (22.0)	16 (20.5)	
>5 per day	21 (13.7)	34 (46.6)		18 (11.0)	52 (66.7)	
SLT holding duration						
Avg min of holding[c]	10.12±7.20	14.17±17.73	0.14[b]	10.46±8.86	13.82±9.50	**0.04[b]**
Never users	103 (67.3)	20 (24.7)	**<0.001[a]**	110 (67.1)	10 (12.8)	**0.001[a]**
≤10 minutes	43 (28.1)	37 (50.7)		44 (26.8)	44 (56.4)	
>10 minutes	7 (4.6)	16 (21.9)		10 (6.1)	24 (30.8)	
Total Yrs. of SLT use						
Avg years of use[c]	31.46±15.41	29.75±13.45	0.55[b]	31.24±14.37	30.82±12.78	0.41[b]
Never users	103 (67.3)	20 (24.7)	**<0.001[a]**	110 (67.1)	10 (12.8)	**<0.001[a]**
≤30 years	26 (17.0)	27 (37.0)		22 (13.4)	34 (43.6)	
>30 years	24 (15.7)	26 (35.6)		32 (19.5)	34 (43.6)	
Lifetime exposure to SLT						
Average Chew-years[c]	21.62±23.38	25.01±20.36	0.43[b]	20.26±22.19	30.53±22.87	**0.01[b]**
Never user	103 (67.3)	20 (24.7)	**<0.001[a]**	110 (67.1)	10 (13.0)	**<0.001[a]**
≤20 chew-years	30 (19.6)	28 (38.4)		35 (21.3)	26 (33.8)	
21-40 chew-years	15 (9.8)	15 (20.5)		13 (7.9)	22 (28.6)	
>40 chew-years	5 (3.3)	10 (13.7)		6 (3.7)	19 (24.7)	

Abbreviations: BQ (Betel Quid).; SLT, Smokeless Tobacco.
[a] p-value derived from chi-square test/Fisher-exact test
[b] p-value derived from t-test.

[c] *Mean with Standard Deviation*
[d] *Chewing habits- Overall chewing habits both with and without SLT*
[e] *Chewing habit with tobacco- such as BQ with Zarda or sadapata, Gul, Panmasala containing tobacco, arecanut with tobacco, sadapata alone.*
[f]*Chewing habit without tobacco- such as BQ without tobacco, areca nut alone, panmasala without tobacco.*

4.2.6.2 Odds ratios for oral cancer of smokeless tobacco use (Both gender)

Table 54 illustrates the odds ratios (ORs) for oral cancer associated with SLT use. The odds ratios were obtained from unconditional logistic regression model where initially SLT was the only independent variable and later adjusted for matching factors (age and gender) and was further adjusted for education status (no-formal education and formal education), employment status (paid work and unpaid work), BMI (continious) and smoking status (never and ever).

The analysis showed that SLT was associated with a highly elevated risk of oral cancer. The present study found a strong association between ever SLT use and oral cancer and the association remained significant even after adjusting for other measures [ORadj: 8.78 (95%CI: 5.14-15.0) (p-value: <0.001)]. The chewing habit without SLT also increased the oral cancer risk but the risk was lower than SLT use, [ORadj: 4.97 (95%CI: 1.98-12.47) (p-value: <0.001)].

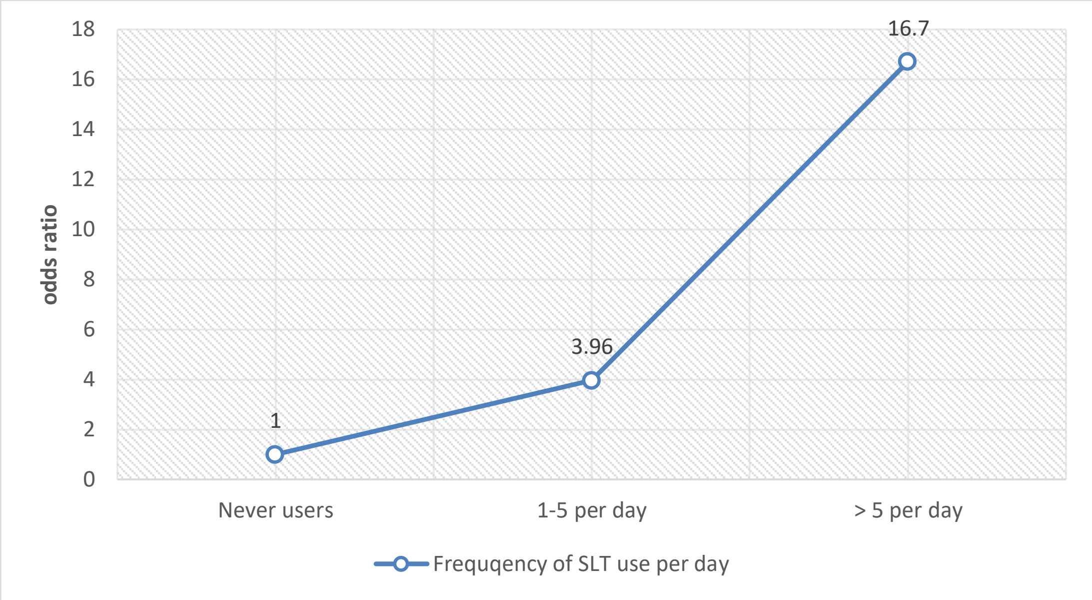


Figure 18: Relationship between frequency of smokeless tobacco use per day and the risk of oral cancer

Both BQ with tobacco and without tobacco increased the oral cancer risk. BQ with Zarda or Sadapata possessed the greatest risk [ORadj: 8.93 (95%CI: 5.23-15.27)] (p-value: <0.001). BQ without tobacco also increased the risk by more than four-fold. Using multiple SLT products simultaneously was associated with a six-fold increased risk of oral cancer when the relative group was non-users [ORadj: 6.47 (95%CI: 1.95-21.46)] (p=0.002).

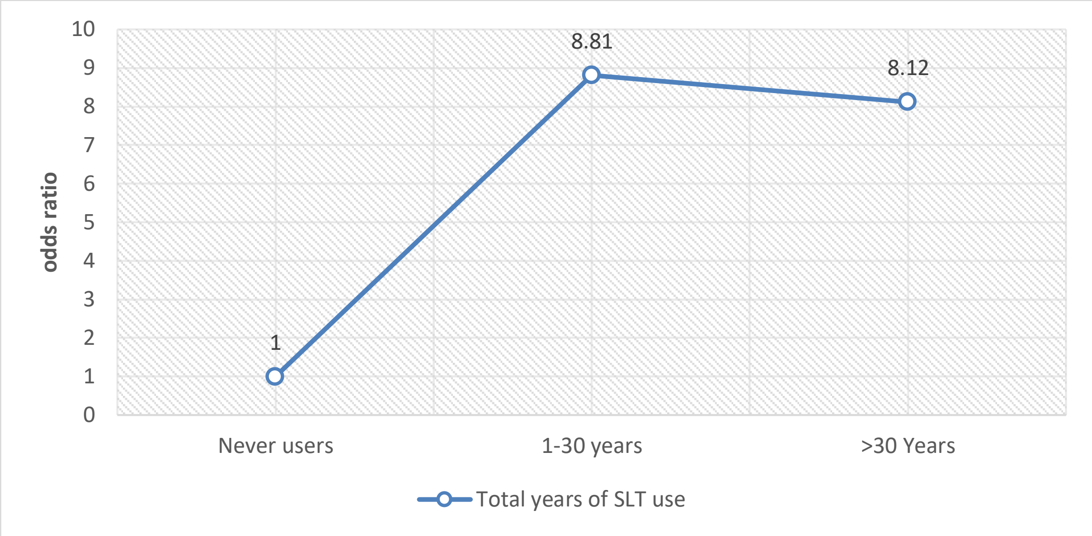


Figure 19: Association between total years of smokeless tobacco use and risk of oral cancer

Though, the linear trend was not statistically significant, when looked across categories, initiating SLT in younger age was associated with higher oral cancer risk. Present study findings showed that participants who started SLT at the age of 20 years old or younger were nine times more likely to develop oral cancer when relative group was never user, ORadj: 9.84 (95%CI: 5.47-17.72)

Use of SLT shows a clear and strong dose-response relationship for several measures: frequency of SLT used per day, the duration of each chewing, and lifetime exposure to SLT use. Consuming SLT one to five times a day increased the oral cancer risk by nearly four-fold, when relative group was non-users and the risk increased to over 16-fold for consuming over five times a day [ORadj: 16.70 (95%CI: 9.08-30.72)] (p-value: <0.001) (see Figure 18). The linear trend was reamined statistically significant after adjusting for other covariates. Keeping SLT longer in mouth increased the oral cancer risk substantialy. Adjusted odds ratio for oral cancer was ORadj=15.18 (95%CI: 7.05-32.68) for holding SLT for over 10 minutes (see Figure 20).

Though the liner trend was not statistically significant, the adjusted odds ratio for oral cancer and total years of SLT use whether referred to 1-30 years or more than 30 years exceeded eight folds and remained statistically significant after adjustment for possible confounders (see Figure 19). Lifetime cumulative exposure to SLT was associated with oral cancer risk and shown strong dose-response relationship. The adjusted odds ratio for 20 chew-years or less was six folds and rising progressively to over 26-folds for 40 chew years and the linear trend was statistically significant in fully adjusted model.

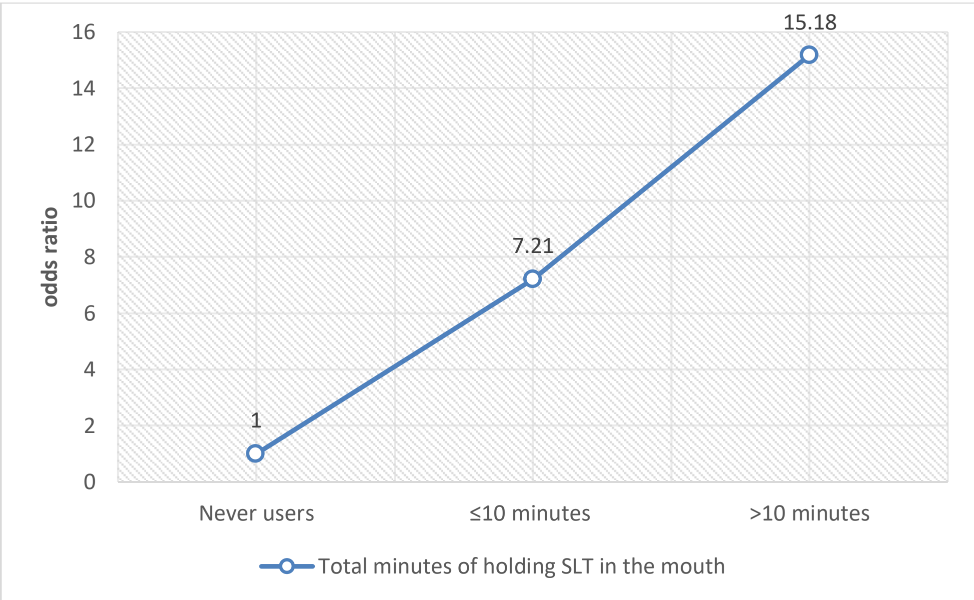


Figure 20: Association between total minutes of smokeless tobacco holding in the mouth and risk of oral cancer

Table 54: Odds ratios with 95% confidence interval for oral cancer from smokeless tobacco use among both gender

Categories	Cases	Control	Crude OR (95% CI) [a]	Adjusted OR (95% CI) [b]	Fully adjusted OR (95% CI) [c]	*P-value[d]*
Chewing habits						
Never	30	213	Reference	Reference	Reference	***<0.001***
Ever users	139	125	7.90 (5.02-12.40)	8.28 (5.22-13.14)	7.86 (4.70-13.14)	
Current users	115	89	9.17 (5.72-14.70)	9.37 (5.82-15.08)	8.59 (5.07-14.55)	***<0.001***
Past users	24	36	4.73 (2.49-9.00)	5.01 (2.57-9.77)	5.30 (2.53-11.11)	
Chewing habits with SLT[f]						
Never	30	213	Reference	Reference	Reference	***<0.001***
Ever chewing	121	104	8.26 (5.20-13.13)	8.61 (5.36-13.83)	8.78 (5.14-15.0)	
Chewing habits without SLT						
Never	30	213	Reference	Reference	Reference	***0.001***
Ever chewing	18	21	6.09 (2.91-12.7)	6.38 (2.99-13.61)	4.97 (1.98-12.47)	
Type of chewing products						
None	30	213	Reference	Reference	Reference	***<0.001***
BQ with Zarda/sadapata	116	99	8.32 (5.22-13.28)	8.74 (5.42-14.07)	8.93 (5.23-15.27)	
BQ without tobacco	18	21	6.09 (2.91-12.71)	6.38 (3.04-13.42)	4.43 (1.94-10.10)	
Gul/Panmasala	5	5	7.10 (1.94-25.98)	7.38 (2.01-27.13)	6.39 (1.39-29.35)	
Multiple SLT use						
No	157	334	Reference	Reference	Reference	***0.002***
Yes	12	4	6.38 (2.02-20.10)	6.38 (2.01-20.21)	6.47 (1.95-21.46)	

Categories	Cases	Controls	Crude OR (95% CI) [a]	Adjusted OR (95% CI) [b]	Fully adjusted OR (95% CI) [c]	*P-value* [d]
Age at SLT initiation [f]						
Never users	30	213	Reference	Reference	Reference	***<0.001***
≤20 years old	74	58	9.06 (5.42-15.15)	9.59 (5.66-16.25)	9.84 (5.47-17.72)	
21-30 years old	31	30	7.34 (3.90-13.79)	7.63 (4.02-14.48)	6.98 (3.48-13.98)	
>30 years old	16	16	7.10 (3.22-15.67)	7.19 (3.25-15.88)	7.31 (3.04-17.55)	
P-for trend			0.61	0.67	0.48	
Freq of SLT per day [f]						***<0.001***
Never users	30	213	Reference	Reference	Reference	
1-5 per day	35	65	3.82 (2.81-6.70)	3.99 (2.26-7.05)	3.96 (2.13-7.37)	
> 5 per day	86	39	15.66 (9.14-26.81)	16.68 (9.60-28.97)	16.70 (9.08-30.72)	
P-for trend			***<0.001***	***0.001***	***0.001***	
Duration of holding SLT [f]						
Never users	30	213	Reference	Reference	Reference	***<0.001***
≤10 minutes	81	87	6.61 (4.07-10.76)	6.92 (4.22-11.37)	7.21 (4.18-12.45)	
>10 minutes	40	17	16.71 (8.43-33.11)	18.24 (9.04-36.82)	15.18 (7.05-32.68)	
P-for trend			***0.02***	***0.01***	***0.04***	
Total Years of SLT use [f]						
Never users	30	213	Reference	Reference	Reference	***<0.001***
1-30 years	61	48	9.02 (5.27-15.45)	8.91 (5.19-15.28)	8.81 (4.87-15.94)	
>30 years	60	56	7.61 (4.49-12.90)	8.25 (4.62-14.74)	8.12 (4.29-15.38)	
P-for trend			0.59	0.61	0.73	
Lifetime exposure to SLT [f]						***<0.001***
Never user	30	213	Reference	Reference	Reference	
≤20 chew-years	54	65	5.90 (3.49-9.98)	6.08 (3.58-10.32)	6.01 (3.36-10.76)	
21-40 chew-years	37	28	9.38 (5.04-17.48)	10.70 (5.61-20.42)	10.58 (5.18-21.58)	
>40 chew-years	29	11	18.72 (8.48-41.34)	23.53 (10.18-54.39)	26.84 (10.81-66.62)	
P-for trend			***0.02***	***0.004***	***0.006***	

Abbreviations: CI, confidence interval; N, number; OR, odds ratio.; SLT, Smokeless Tobacco; BQ, Betel Quid

[a] *Crude OR: OR and 95% CI were calculated using unconditional logistic regression*
[b] *OR and 95% CI were calculated using unconditional logistic regression, adjusted for matching factors gender and age*
[c] *OR and 95% CI were calculated using unconditional logistic regression, adjusted for matching factors [a], education status (cat), employment status (cat), Smoking status (cat), BMI (cat)*
[d] *p-values for fully adjusted model*
[e] *p-values for the linear trend was derived from including the variable as a continuous variable in the unconditional regression model.*
[f] *Analysis excluding chewing products without tobacco*

4.2.6.3 Odds ratios for oral cancer of smokeless tobacco use among men

Table 55 shows the odds ratios for oral cancer from SLT use among male participants. Odds ratios were obtained from the unconditional logistic regression model. Three ORs were presented. First, crude or unadjusted ORs (only target independent variable), second ORs adjusted for matching factor age and further adjusted for education status (no-formal education and formal education), employment status (paid work and unpaid work), BMI (continuous) and smoking status (never and ever).

The ORs for oral cancer and SLT use among male ever SLT users relative to never users exceeded five and remained statistically significant after adjustment. For the past users the odds ratio was: ORadj: 5.29 (95%CI: 2.62-10.67). Similarly, chewing habits without SLT also increased the oral cancer risk, ORadj: 4.46 (95%CI: 1.06-18.80). However, risk of oral cancer was lower among non-tobacco chewers compared to chewing habits with tobacco (see table 55)

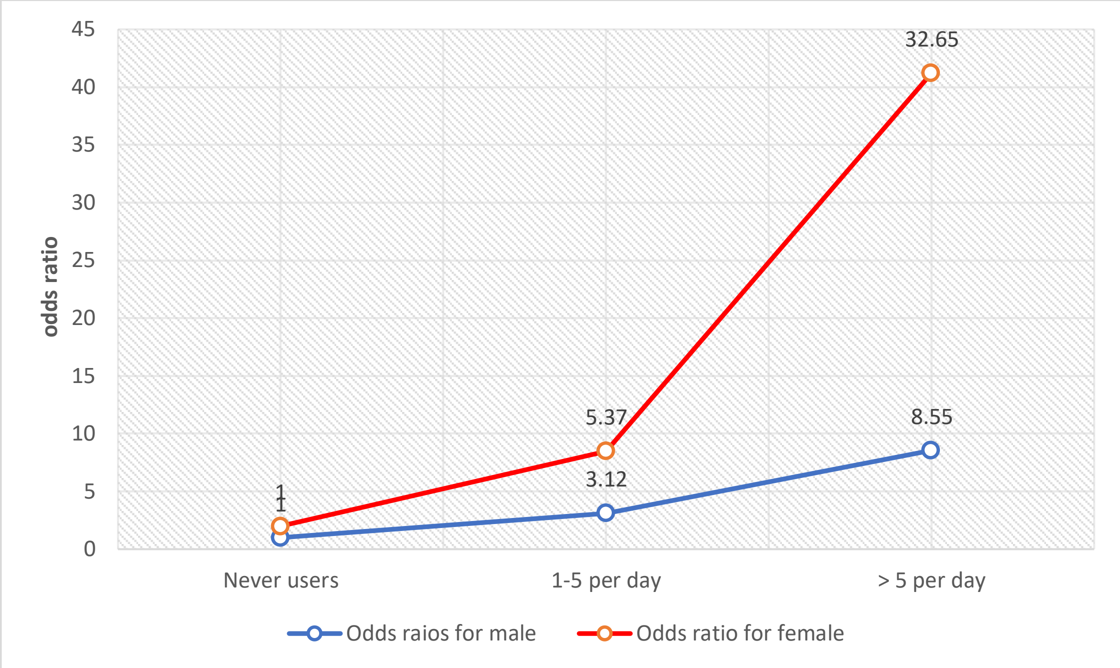


Figure 21: Relationship between frequency of smokeless tobacco use per day and oral cancer risk (comparison between male and female)

Among men, both BQ with Zarda or Sadapata and BQ without tobacco increased oral cancer risk– ORadj=5.89 (95%CI: 2.87-12.10) and ORadj=2.78 (95%CI: 0.81-9.51) respectively. However, the estimate for BQ without tobacco was not precise, with a large confidence interval due to an inadequate observation.

Starting SLT at a younger age was related with a greater risk of oral cancer. Men who started using SLT at the age 20 or below were six times more likely to develop oral cancer compared to those who did not use SLT, ORadj= 6.12 (95%CI: 2.67-13.95), Whereas the ORs for initiating SLT at the age after 30 years old was only, ORadj= 4.50 (95%CI: 1.36-14.85). However, the linear trend was statistically insignificant.

A strong dose-response relationship was observed between frequency of SLT use and oral cancer incidence. Adjusted odds ratio for men who consumed SLT 1-5 times a day was, ORadj= 3.12 (95%CI: 1.34-7.21) rising to more than eight-fold for those consuming SLT more than five times a day (see figure 21). Similarly, holding

SLT longer in mouth increased the oral cancer risk. However, the linear trend was not statistically significant (see Table 55).

The adjusted ORs for the total duration of SLT was more than four-fold for those consumed SLT for less than 30 years and increased to more than six-fold for those consumed SLT over 30 years. Additionally, lifetime cumulative exposure showed four- fold increased risk for 20 or less chew-years and climbed to nearly 13-fold for more than 40-chew-years (see figure 24)

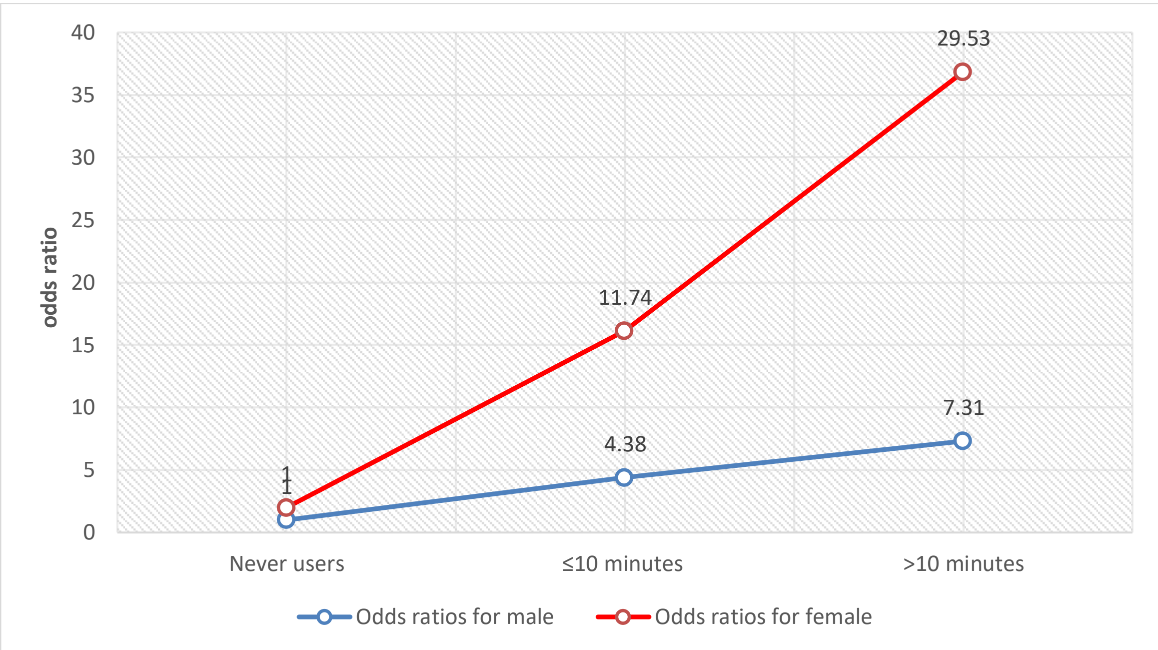


Figure 22: Relationship between total minutes of retaining smokeless tobacco in the mouth and risk of oral cancer (comparison between male and female

Table 55: Odds ratios with 95% Confidence interval for oral cancer from smokeless tobacco use among men (81 cases and 162 controls)

Categories	Cases	Control	Crude OR (95% CI) [a]	Adjusted OR (95% CI) [b]	Fully adjusted OR (95% CI) [c]	***P-value*** [d]
Chewing habits						
Never	20	103	Reference	Reference	Reference	***<0.001***
Ever users	61	59	5.32 (2.93-9.68)	5.32 (2.92-9.72)	5.19 (2.60-10.36)	
Current users	48	45	5.49 (2.93-10.30)	5.49 (2.92-10.30)	5.07 (2.47-10.41)	***<0.001***
Past users	13	14	4.78 (1.96-11.69)	4.77 (1.93-11.79)	5.71 (2.03-16.08)	
Chewing habits with SLT [f]						
Never	20	103	Reference	Reference	Reference	***<0.001***
Ever chewing	53	50	5.46 (2.95-10.01)	5.42 (2.92-10.06)	5.29 (2.62-10.67)	
Chewing habits without SLT						
Never	213	30	Reference	Reference	Reference	***0.04***
Ever chewing			4.59 (1.58-13.29)	4.43 (1.52-12.94)	4.46 (1.06-18.80)	
Type of chewing products [f]						
None	20	103	Reference	Reference	Reference	***<0.001***
BQ Zarda/Sadapata	48	46	5.37 (2.87-10.06)	5.38 (2.87-10.10)	5.89 (2.87-12.10)	
BQ without tobacco	8	9	4.58 (1.58-13.29)	4.59 (1.58-13.35)	2.78 (0.81-9.51)	
Gul/Panmasala	2	2	5.15 (0.68-38.73)	5.15 (0.68-38.75)	2.92 (0.21-40.91)	
Age at SLT initiation [f]						
Never users	20	103	Reference	Reference	Reference	***<0.001***
≤20 years old	28	26	5.55 (2.71-11.36)	5.52 (2.69-11.31)	6.12 (2.67-13.95)	
21-30 years old	16	17	4.85 (2.10-11.16)	4.76 (2.04-11.06)	4.61 (1.78-11.88)	
>30 years old	9	7	6.62 (2.21-19.85)	6.61 (2.20-19.82)	4.50 (1.36-14.85)	
P-for trend			*0.97*	*0.94*	*0.51*	

Categories	**Cases**	**Control**	**Crude OR (95% CI) [a]**	**Adjusted OR (95% CI) [b]**	**Fully adjusted OR (95% CI) [c]**	***P-value[d]***
Freq of SLT per day[f]						
Never users	20	103	Reference	Reference	Reference	***0.005***
1-5 per day	19	29	3.37 (1.59-7.15)	3.37 (1.59-7.15)	3.12 (1.34-7.21)	
> 5 per day	34	21	8.34 (4.04-17.21)	8.33 (4.01-17.32)	8.55 (3.75-19.48)	
P-for trend[e]			0.10	0.08	0.10	
Duration of holding SLT[f]						
Never users	20	103	Reference	Reference	Reference	***<0.001***
≤10 minutes	37	43	4.43 (2.31-8.49)	4.49 (2.31-8.50)	4.83 (2.30-10.11)	
>10 minutes	16	7	11.77 (4.29-32.29)	11.75 (4.24-32.52)	7.31 (2.38-22.61)	
P-for trend[e]			0.18	0.15	0.31	
Total Years of SLT use[f]						
Never users	20	103	Reference	Reference	Reference	
1-30 years	27	26	5.35 (2.60-11.01)	5.40 (2.61-11.20)	4.85 (2.16-10.89)	***<0.001***
>30 years	26	24	5.58 (2.68-11.61)	5.44 (2.51-11.82)	5.93 (2.45-14.35)	
P-for trend[e]			0.55	0.79	0.81	
Lifetime exposure to SLT[f]						
Never user	20	103	Reference	Reference	Reference	***<0.001***
≤20 chew-years	28	30	4.81 (2.38-9.71)	4.80 (2.37-9.70)	4.34 (1.98-9.51)	
21-40 chew-years	15	15	5.15 (2.18-12.18)	5.20 (2.16-12.52)	5.65 (2.11-15.09)	
>40 chew-years	10	5	10.3 (3.18-33.37)	10.48 (3.11-35.26)	13.34 (3.41-52.15)	
P-for trend[e]			0.3	0.17	0.19	

Abbreviations: CI, confidence interval; N, number; OR, odds ratio.; SLT, Smokeless Tobacco
[a] Crude OR: OR and 95% CI were calculated using unconditional logistic regression
[b] OR and 95% CI were calculated using unconditional logistic regression, adjusted for age
[c] OR and 95% CI were calculated using unconditional logistic regression, adjusted for, age, education status, employment status, smoking status (never, ever), BMI (continuous).

[d] *P-value derived from entering the independent variables as a categorical variable in the logistic model.*
[e] *P-for trends derived from entering predictor variables as continuous variables in the logistic model.*
[f] *analysis excluding chewing products without tobacco*

4.2.6.4 Odds ratios for oral cancer of smokeless tobacco use among women

Table 56 represents odds ratios with 95% confidence interval for oral cancer from SLT use among women. Odds ratios were derived from the unconditional logistic regression model. Three ORs were reported. Firstly, crude or unadjusted ORs (only target independent variable), second ORs adjusted for matching factor age and third ORs were derived from further adjustment for education status (no-formal education and formal education), employment status (paid work and unpaid work), BMI (continuous).

The risk of oral cancer from ever using SLT use among women is more than double compared to men, ORadj=14.33 (95%CI: 6.33-32.42) and ORadj=5.29 (95%CI: 2.62-10.67) respectively. The association remained statistically significant ($p<0.001$) after adjusting for other measures. Regarding the types, BQ with Zarda/sadapata was associated with the highest risk, ORadj= 14.03 (95%CI: 6.10-32.25). In addition, BQ without tobacco also increased the oral cancer risk but much lower compared BQ with tobacco, ORadj= 8.58 (95%CI: 2.66-27.74).

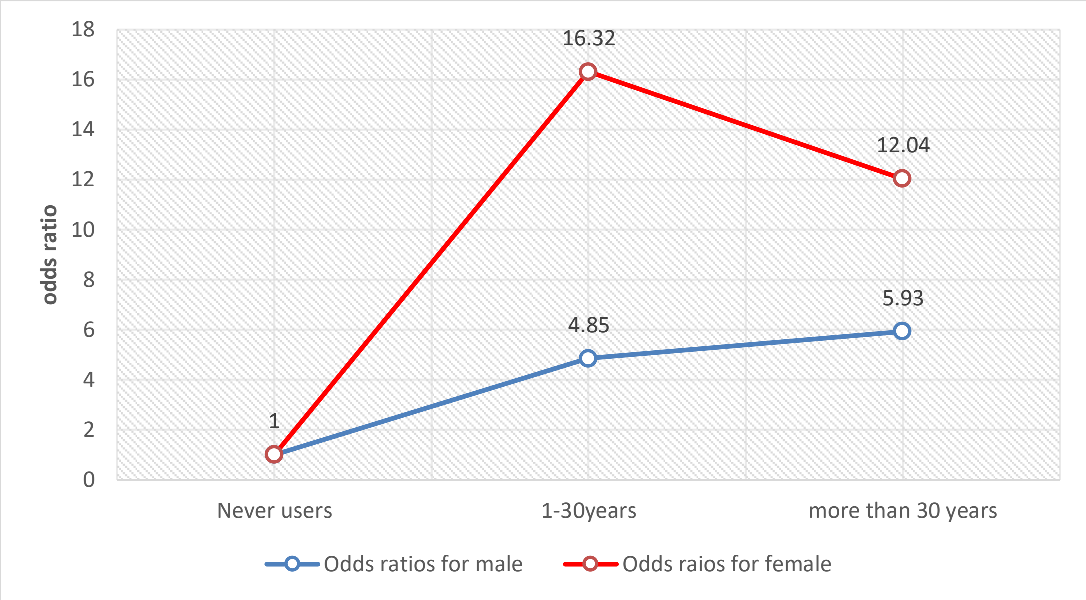


Figure 23: Relationship between total years of smokeless tobacco use and risk of oral cancer (comparison between male and female)

A strong dose-response relationship was observed for frequency of SLT use. Women who chewed SLT up to five times a day had the odds ratio of, ORadj= 5.37 (2.07-13.89) and that increased to nearly 33-fold for chewing SLT more than five times a day (see Figure 21). The linear trend remained significant after adjusting for other covariates. Similar to men, women who started SLT at the age 20 years old or younger had the highest risk compared to non-users. The adjusted OR was 16.65 (95% CI: 6.83-40.55) when relative group was never users.

Holding SLT longer inside mouth increased oral cancer risk substantially. Among women, those reported holding SLT over 10 minutes had 29 times higher odds of developing oral cancer. The adjusted odds ratio was, ORadj: 29.53 (95%CI: 9.84-88.56) (see Figure 22).

The lifetime exposure to SLT which was expressed in chew-years, showed strong dose-response relationship. The adjusted odds of oral cancer for those had 20 or less chew-years was, ORadj= 8.96 (95%CI: 3.65-22.01) and increased to, ORadj=20.91 (95%CI: 7.24-60.39) for those with 21-40 chew-years. The liner trend remained significant after adjusting for other measures (see figure 24)

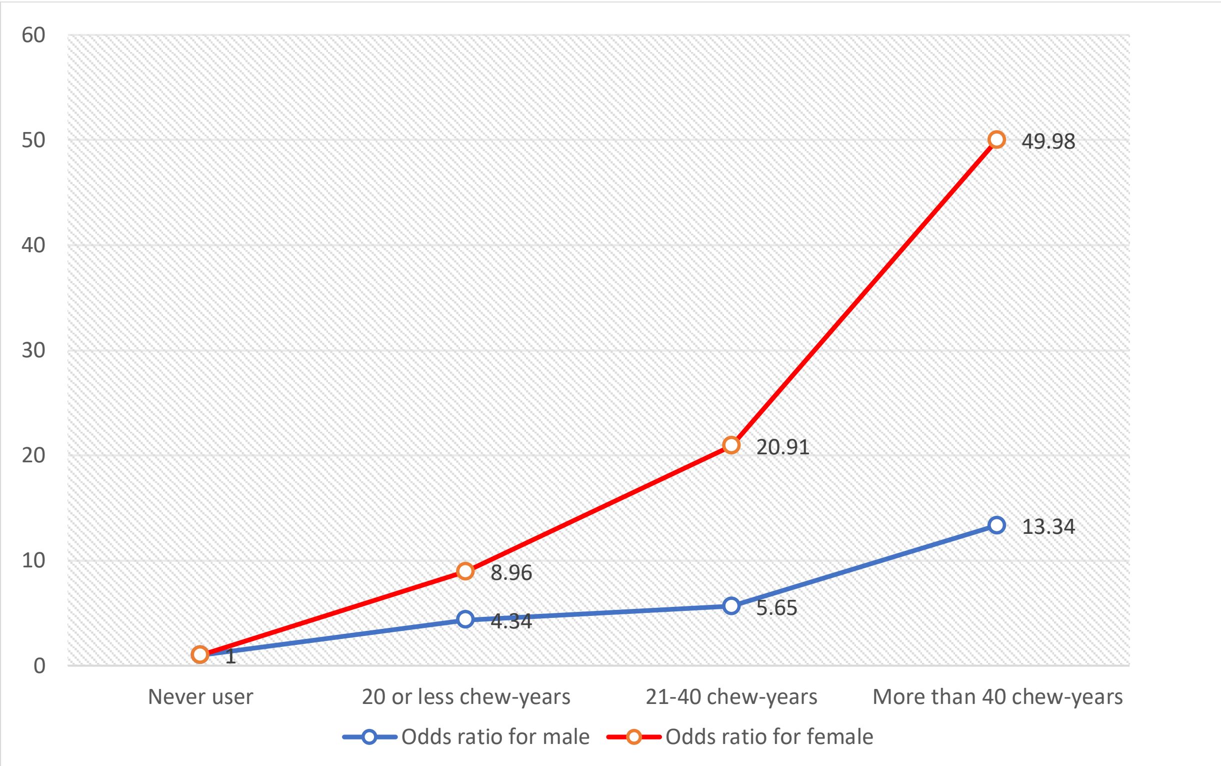


Figure 24: Relationship between lifetime chew-years and risk of oral cancer (comparison between male and female)

Table 56: Odds ratios with 95% confidence interval for oral cancer of smokeless tobacco use among women (88 cases and 176 controls)

Categories	Case	Control	Crude OR[a] (95% CI)	Adjusted OR [b] (95% CI)	Fully adjusted OR[c] (95% CI)	*P-value[d]*
Chewing habit						
Never	10	110	Reference	Reference	Reference	***<0.001***
Ever chewing	78	66	13.00 (6.29-26.86)	14.88 (7.00-31.62)	12.79 (5.69-28.72)	
Current chewing	67	44	16.75 (7.90-35.49)	17.46 (8.16-37.37)	15.10 (6.65-34.28)	***<0.001***
Past chewing	11	22	5.50 (2.08-14.52)	6.37 (2.25-18.00)	5.62 (1.86-17.03)	
Chewing with SLT[f]						
Never	10	110	Reference	Reference	Reference	***<0.001***
Ever chewing	68	54	13.85 (6.61-29.01)	16.07 (7.41-34.81)	14.33 (6.33-32.42)	
Chewing without tobacco						
Never	10	110	Reference	Reference	Reference	
Ever chewing	10	12	9.17 (3.18-26.46)	9.72 (3.25-29.05)	10.70 (3.27-34.99)	
Type of chewing products						
None	10	110	Reference	Reference	Reference	***<0.001***
BQ with Zarda/Sadapata	65	51	14.02 (6.66-29.50)	16.17 (7.46-35.03)	14.03 (6.10-32.25)	
BQ without tobacco	10	12	9.17 (3.18-26.45)	10.37 (3.50-30.30)	8.58 (2.66-27.74)	
Gul/Panmasala	3	3	11.00 (1.96-61.82)	12.20 (2.13-69.86)	10.89 (1.63-72.24)	
Age at SLT initiation[f]						
Never users	10	110	Reference	Reference	Reference	***<0.001***
≤20 years old	46	32	15.81 (7.18-34.81)	19.71 (8.48-45.83)	16.65(6.83-40.55)	
21-30 years old	15	13	12.69 (4.74-33.99)	14.53(5.29-39.92)	11.63(4.06-33.34)	
>30 years old	7	9	8.56(2.63-27.87)	8.98 (2.72-29.61)	11.70 (3.22-42.47)	
P-for Trend			0.54	0.39	0.92	

Categories	Case	Control	Crude OR[a] (95% CI)	Adjusted OR[b] (95% CI)	Fully adjusted OR[c] (95% CI)	*P-value[d]*
Freq of SLT per day[f]						
Never users	10	110	Reference	Reference	Reference	***<0.001***
1-5 per day	16	36	4.89 (2.04-11.73)	5.67(2.29-14.02)	5.37 (2.07-13.89)	
> 5 per day	52	18	31.78 (13.71-73.64)	36.93 (15.29-89.20)	32.65(12.84-83.02)	
P-for trend			***0.002***	***0.001***	***0.003***	
SLT holding duration[f]						
Never users	10	110	Reference	Reference	Reference	***<0.001***
≤10 minutes	44	44	11.00 (5.09-23.77)	12.80 (5.74-28.53)	11.74(5.06-27.24)	
>10 minutes	24	10	26.40 (9.89-70.44)	32.61 (11.64-91.32)	29.53(9.84-88.56)	
P-for trend[e]			0.06	***0.04***	0.06	
Total Years of SLT use[f]						
Never users	10	110	Reference	Reference	Reference	***<0.001***
1-30 years	34	22	17.00 (7.33-39.40)	16.67 (7.17-38.76)	16.32 (6.61-40.27)	
>30 years	34	32	11.69 (5.21-26.21)	15.17 (6.01-38.28)	12.04 (4.62-31.32)	
P-for trend			0.86	0.27	0.75	
Lifetime exposure to SLT[f]						
Never user	10	110	Reference	Reference	Reference	***<0.001***
≤20 chew-years	26	35	8.17 (3.59-18.60)	9.54 (4.08-22.28)	8.96 (3.65-22.01)	
21-40 chew-years	23	13	19.46 (7.61-49.77)	26.45 (9.66-72.40)	20.91 (7.24-60.39)	
>40 chew-years	19	6	34.83 (11.33-107.10)	57.50 (16.74-197.49)	49.98 (14.06-177.63)	
P-for trend[e]			***0.02***	***0.004***	***0.009***	

Abbreviations: CI, confidence interval; N, number; OR, odds ratio.; SLT, Smokeless Tobacco; BQ, Betel Quid
[a] Crude OR: OR and 95% CI were calculated using unconditional logistic regression
[b] OR and 95% CI were calculated using unconditional logistic regression, adjusted for age
[c] OR and 95% CI were calculated using unconditional logistic regression, adjusted for, age, education status, BMI (categorical).
[d] P-value derived from entering the independent variables as a categorical variable in the logistic model.
[e] P-for trends derived from entering predictor variables as continuous variables in the logistic model.
[f] analysis excluding chewing products without tobacco

4.2.6.5 Joint effects of smoking and smokeless tobacco among men

None of the female participants reported smoking. Therefore, the joint effects of SLT and smoking was explored for the men only. Table 57 shows the joint effects of smoking and SLT use among men. As shown in the table both SLT and smoking induced a significant increase risk of oral cancer even for subjects who were never been exposed to other habits. The joint effect of smoking and SLT use in the development of oral cancer appeared to be additive. However, present study does not have adequate statistical power to test the interaction between the variables. Therefore, the joint effects findings should be interpreted with caution.

Table 57: Joint effects of smoking and smokeless tobacco use among male participants

Ever smoked	**Ever SLT**	**Cases (n=81)**	**Controls (n=162)**	**Crude ORs (95%CI)**	**Adjusted ORs (95%CI) [a]**
NO	NO	06	72	1.0	1.0
YES	NO	14	31	5.42 (1.91-15.41)	4.18 (1.42-12.26) *
NO	YES	28	38	8.67 (3.28-22.95)	6.78 (2.47-18.67) **
YES	YES	33	21	23.14 (8.07-66.38)	17.23 (5.70-52.01) **

n: total number; ORs: odds ratio; CI: confidence Interval: SLT: smokeless tobacco.

[a] ORs adjusted for age, education status, employment status, and BMI.

** P-Value less than 0.05, ** P-value less than 0.001.*

Measure of interaction on an additive scale: RERI= 17.23 - 6.78 – 4.18 + 1= 7.27, which is > 0 thus suggesting positive interaction in an additive scale.

Measure of interaction on a multiplicative scale: ratio of ORs= 17.23 / 6.78 X 4.18= 0.61, which is <1.0 thus suggesting negative interaction in multiplicative scale.

4.2.7 Population attributable risk associated with smokeless tobacco use

The estimated overall PAF (Population Attributable Fraction) of SLT for oral cancer in Bangladesh was 61%. The gender specific PAF of SLT for oral cancer in Bangladesh was 41% and 76% for men and women, respectively. In addition, dual use of SLT and smoking related PAF for men was 72%. An estimated 8174 incidence cases of oral cancer in Bangladesh are attributable to SLT use (there was an estimated 13,401 new oral cancer cases during 2018). An estimated 3646 incidence oral cancer cases among men were attributable to SLT use alone (Total oral cancer incidence cases for Bangladeshi men were 8,895) and 6378 new oral cancer cases among men were attributable to dual use of SLT and smoking. For women, 3424 incidence cases of oral cancer were attributable to SLT use (Total oral cancer incidence cases for Bangladeshi women were 4506).

Chapter V. Discussion and Conclusion

The overall aim of this PhD study is to examine the factors contributing to adolescent SLT use in Bangladesh and the role of SLT in oral carcinogenesis amongst Bangladeshi adults. An adolescent cross-sectional survey and a hospital-based case-control study were conducted to attain the research goals. This chapter will illustrate and interpret the key findings of the study and compare the findings with the existing literature in the field. This will be followed by an analysis of the key strengths and limitations of the study, public health implications, recommendations for public health actions and future research, and finally, a brief conclusion.

5.1 Significant findings of the adolescent cross-sectional survey

5.1.1 Practice and Patterns of smokeless tobacco use

The first objective of the adolescent cross-sectional survey was to investigate the current practice and pattern of SLT use among 13-15-year-old rural adolescents in Bangladesh. The findings indicate a rather low current incidence of SLT use among rural Bangladeshi students, with only 3.7% of students being current users and 9.5% of adolescents having ever tried SLT. This was somewhat less prevalent than the previous Global Youth Tobacco Survey (GYTS) results in Bangladesh (4.5%) (WHO, 2015) – which is probably due to the recent implementation of the 15% value added tax (VAT) and 30% supplementary duty on SLT products (Nargis, Hussain and Fong, 2014). The positive association between tax increases and decline in adolescent tobacco use was reported in a previous study (Levy *et al.,* 2017).

The gender differences in adolescent SLT use is a well-established factor. Rural Bangladeshi boys are the main users of SLT, as has been found in the studies conducted in other South Asian countries, e.g. Bhutan, India, Pakistan and Myanmar (Sinha *et al*., 2014; Chatterjee *et al.,* 2016; Bhaskar *et al.,* 2016; Hussain *et al.,* 2017; Rinchen and Taneepanichskul, 2018). However, a study of the African region reported the opposite, as they found that girls were the leading users of SLT (Ranatao and Ayo-Yusuf, 2012).

A previous Global Adult Tobacco Survey report showed that most Bangladeshi adults start using SLT in their 30s (WHO, 2009). Rather unexpectedly, rural adolescents try SLT at a young age, in some cases as early as seven years old. However, the majority of students tried SLT at the age of 12 or younger, which ties in well with previous studies, which found that most adolescents try SLT between the age of 10 and 13 (Rozi and Akther 2007; Kumar *et al.,* 2014; Veeranki *et al.,* 2015; Chatterjee *et al.,* 2016; Hussain *et al.,* 2017;).

Regarding the type and sources of SLT, Zarda was the most commonly used SLT by rural adolescents, as it was with Bangladeshi adults (Huque *et al.,* 2017). This was also observed in neighbouring countries like Nepal and Sri Lanka (Sinha *et al.,* 2014). The present study found that the major source of SLT for rural Bangladeshi adolescents was informal/social connections. More than 40% (12) current users got SLT from social connections and 34% (10) students from commercial sources. This finding validates the results of the previous studies, which suggested that the majority of adolescents got SLT from informal or social connections, followed by commercial sources (Huhtala *et al.,* 2006; Kaestle *et al*., 2009; Warren, Smalley, and Barefoot, 2015).

Regarding SLT accessibility, the results of the present study indicate that most adolescents were able to buy SLT without any restrictions. This striking finding showed that 86% of the current users were able to buy SLT without restriction. Bangladesh has a Tobacco Control Act (TCA) that restricts the sale of tobacco products, including SLT, by or to minors (WHO, 2013b). The present study findings indicate that there is poor implementation of the law in rural areas of Bangladesh. A similar picture was revealed in a recent GYTS report from Bangladesh, where they found 97.8% students (13-15) were not refused tobacco when they tried to buy it (Islam *et al.,* 2016). This study supports evidence from previous reviews, which found that poor implementation of tobacco control law is widespread in LMICs (Sinha *et al.,* 2017).

Poor implementation of the current tobacco control law is also evident from another key finding of the present study, that over 45% of all SLT users did not see any health warnings on the SLT packages. Based on the new Tobacco Act amendment 2013, SLT manufacturers are required to have written health warnings and graphic images that cover at least 50% of the product packaging (WHO, 2013b). However, a previous study by Siddiqi *et al*., (2016) also reported there was poor implementation of this law in Bangladesh.

The present study found that over 89% of current users wanted to quit SLT now – 34% had tried but were unsuccessful – however, professional help was not available. Instead, most of the help was offered by friends and family. The non-existence of SLT cessation services in Bangladesh has also been reported in a previous Global Adult Tobacco Survey (WHO, 2017).

5.1.2 Knowledge and awareness

The second objective of the cross-sectional study was to determine the knowledge and perception of the ill effects of SLT use. There was good overall knowledge of the harm that SLT caused – over 75% of the respondents thought SLT use was bad for their health. Regarding the adverse effects of SLT use, over 50% of adolescents knew that SLT causes white patches in the mouth and over 60% of respondents knew that SLT causes oral cancer, gum diseases and heart disease. These findings support the results of other studies carried out in neighbouring countries like India, where they found that most adolescents knew about the adverse effects of SLT use (Goyal and Bhagawati, 2016; Metgud *et al.,* 2018).

Over 40% of students were unaware that SLT products contained nicotine. This finding is comparable with a study conducted in Tanzania, where 50% of students were unaware that SLT products contained nicotine (Kaduri *et al.,* 2008). Regarding the perceived severity of SLT, over 25% of students thought it was less harmful compared to smoking tobacco and 32% of respondents were unaware of the relative harm of SLT compared to traditional smoking tobacco. These results suggest that despite having a good knowledge of the adverse effects of SLT, misconceptions about its use still exist. These findings are in line with previous studies, where the belief that SLT is less harmful than cigarettes was widely prevalent among adolescents (Persoskie *et al.,* 2017; Randolph, 2017; Walker *et al.,* 2018).

Regarding the knowledge index, 54.2% (428) of respondents had a good knowledge of the adverse effects of SLT. Though non-users were more aware of SLT-related harms than users and males than females. In addition, respondents with unfavourable attitudes, such as adolescents who would use SLT if it were offered by a friend, had less knowledge than students with favourable attitudes ($p=0.003$). Similarly, adolescents who thought it was not difficult to quit using SLT had significantly poorer knowledge compared to those that thought the opposite ($p<0.0001$).

5.1.3 Predictors of current smokeless tobacco use

The third objective of the adolescent cross-sectional survey was to locate the key predictors of current SLT use. The following measures were ($p<0.05$) associated with current SLT use in adolescents: age, self-efficacy, perceived barriers, perceived benefits, and perceived severity. Their father's profession was significantly associated in the univariate analysis but lost its significance in the multivariate analysis.

Age was a significant predictor of current SLT use, which was consistent with previous studies, as adolescents aged 14 and above were six times more likely to be a current SLT user compared to those younger than 14 (OR-6.59; 95%CI: 1.93-22.50). The increasing trend of older adolescents currently using SLT is consistent with previous studies in the US and South Asia (Tomar and Giovino, 1998; Reddy *et al.,* 2006; Rozi and Akther, 2007; Agaku *et al*., 2013; Chaffee *et al*., 2019). However, this is contradictory to studies from the African region, where SLT prevalence in adolescents decreases with age (Rudatisikari *et al*., 2010; Veeranki *et al.,* 2015).

In this study, 'self-efficacy' was one of the significant predictors of current SLT use. Adolescents who would use SLT if offered by a friend were nearly six times more likely to be current SLT users than those who would not (OR-5.79, 95% CI = 1.62-20.62). This finding is consistent with previous studies (Rantao and Ayo-Yusuf, 2012; Kumar *et al.,* 2014) where lower refusal self-efficacy was associated with increased SLT use amongst adolescents. As predicted by Bandura's Social Cognitive Theory, individuals with a high level of internal locus of control and self-efficacy have more control over negative behaviour (e.g. tobacco use) (Bandura, 1989). This suggests that improving self-efficacy through behavioural interventions can enhance the individual's success in quitting SLT or prevent its future use (Siddiqi *et al.,* 2016).

The findings also showed that adolescents who perceived that quitting SLT is easy were three times more likely to be current SLT users, compared to those who perceived the opposite. This suggests that adolescents who are current SLT users generally know the adverse effects of SLT use but are unaware of its addictive nature. In other words, adolescents who are current SLT users are less concerned about the health consequences because they think they can quit SLT easily. Previous studies have shown that adolescents have adequate knowledge of the long-term effects of SLT use (Goyal and Bhagawati, 2016; Metgud *et al.,* 2018). The findings of the present study show that 59% of the respondents thought it was not difficult to quit SLT after they had started using it, thus, exemplifying the adolescents' misconception about the addictive nature of SLT use.

Adolescents who thought there were benefits of SLT use were four times more likely to be current SLT users compared to those that thought the opposite. The study findings are in line with the previous studies (Aryal *et al.*, 2013; Liu *et al.*, 2015; Morrell *et al.,* 2016). This finding provides further support for the argument that adolescents are usually subject to an optimism bias while becoming a regular tobacco user. This view is consistent with the Health Belief Model (HBM), which predicts that individuals who perceive that SLT will not harm their body and even has benefits, are susceptible to SLT use (Glanz *et al.,* 2015).

The present study found that lower harm perception was positively associated with current SLT use – adolescents who thought that SLT was less harmful than smoking tobacco were nearly three times more likely to be current SLT users compared to those who thought the opposite (OR- 2.79; 95%CI: 1.01-7.61). These findings are consistent with previous cross-sectional studies which found that low perception of harm is associated with SLT use in adolescents (Smith *et al.*, 2015; Persoskie *et al.,* 2017; Parker *et al.,* 2018;). Future efforts should be made to raise awareness of SLT's addictive nature.

5.2 Significant findings of the hospital-based case-control study

5.2.1 Risk of oral cancer associated with smokeless tobacco use

Data from this hospital-based case-control study showed there was an elevated risk of oral cancer amongst SLT users relative to non-users, which further supports the IARC's evidence that SLT use causes oral cancer in humans (IARC, 2012). Ever using SLT elevated the oral cancer risk by nearly eight-fold when the relative group were non-users. However, the former SLT users experienced a much lower risk compared to ever users. The magnitude of the risk remained significant after an adjustment had been made for other demographics and risk factors and stratified analysis by gender. The eight-fold increased risk of oral cancer among ever SLT users in the present study was in line with the odds reported in the systematic review and metanalysis from South Asia (OR: 7.46; 95%CI: 5.86-9.50) (Gupta and Johnson, 2014) and the case-control study from India (OR: 8.51, 95%CI: 4.90-14.77) (Gupta, Kumar and Johnson, 2017), though the Pakistan study reported there were higher odds of oral cancer associated with SLT use (20-fold) (Khan *et al.,* 2017). It is likely that the possible reason for the higher odds reported in the Pakistani study was down to the type of SLT product (Naswar) used.

With regard to gender, women are more likely to develop oral cancer than men. They are also more susceptible to develop SLT induced oral cancer than men. Previous studies from the subcontinent have also reported the risk of oral cancer is higher in women. A systematic review of case-control studies in India reported that women had a 12-fold increased risk of oral cancer from SLT use, whereas the odds were only five-fold for men (Sinha *et al.*, 2016). These higher odds are attributed to differences in their habits. For example, women used SLT more frequently and longer than men. It is also worth noting that female cases in the present study started using SLT two years earlier than men, on average. Moreover, they used SLT more frequently, with 66% of women using SLT more than five times a day whereas only 46% of men did. The higher prevalence of cervical cancer among Bangladeshi women (Haque *et al.*, 2017) may be down to the Human Papilloma Virus (HPV), which is also an established risk factor for oral cancer (Herrero *et al.,* 2003).

In terms of the various SLT types, this study supports the IARC classification of chewing 'BQ with tobacco' and 'BQ without tobacco', both of which are causes of oral cancer. The present study findings show that chewing BQ with zarda or sadapata increase the risk of oral cancer more than eight-fold. Similar findings were reported in studies from neighbouring countries. A previous case-control study from India reported an 11-fold increased risk of oral cancer associated with chewing BQ with tobacco (Madathil *et al.*, 2016).

The present study found there was an increased risk of oral cancer from chewing BQ without tobacco. However, the magnitude of the risk was lower than chewing BQ with tobacco. For the present study, the odds ratio for oral cancer of chewing BQ without tobacco was OR= 4.43 (95%CI:1.94-10.10). Though the risk of contracting oral cancer from BQ without tobacco was similar to the other studies from the South Asian region, the magnitude of the risk was lower than the risk reported in the Pacific region. A systematic review and metanalysis of case-control studies from India and the Pacific region reported that the risk of oral cancer in the Indian subcontinent was mRR: 2.56 compared to mRR: 10.98 in the Pacific region (Guha *et al.*, 2014). Similarly, a hospital-based case-control study in Taiwan reported a positive association between BQ without tobacco and oral cancer, and the reported odds ratio was 6.31 (95%CI: 3.98-10.00) (Wu *et al.*, 2016). The higher magnitude of the oral cancer risk reported in Taiwan and China compared to this study may be due to the large number of BQ chewed per day, or a variation in the BQ preparation, such as the type of areca nut or slaked lime used with BQ. For example, a case-control study from Taiwan reported that red slaked lime had the strongest effect on oral cancer risk and was associated with a ten-fold increased risk of oral cancer (Loyha *et al.*, 2012). Also, in China and Taiwan, unripe areca nut and betel inflorescence are commonly added with BQ, whereas mature areca nuts are used in the Indian subcontinent. Previous study results have suggested that unripe areca nut and betel inflorescence are associated with a higher oral cancer risk (Ko *et al.*, 1995; Wu *et al.,* 2016).

The findings in the present study clearly demonstrated that the risk of oral cancer rises with the increased frequency and duration of SLT use, thus further strengthening the evidence for causality between SLT use and oral cancer risk. For the present study, a clear and strong dose-response between the relationship frequency and duration of SLT use and the dose-response relationship was strongest among women.

The present study's findings showed there is a higher oral cancer risk that is associated with both the intensity and duration of SLT use. After controlling for potential confounders, the risk of oral cancer was found to increase with the increased frequency of its use. The linear trend was significant for both men and women. A similar trend had been reported in the previous studies. A case-control study from India showed that consuming SLT ten times a day was associated with a 42-fold increased risk of oral cancer, whereas the risk was only two-fold when SLT was used five times or less (Gupta *et al.,* 2017). Another hospital-based case-control study by Madathil *et al.,* (2016) showed that chewing BQ ten times a day was associated with an eight-fold increased risk of oral cancer and chewing BQ once a day was associated with only a four-fold increase. The present study found that men using SLT more than five times a day was associated with an eight-fold increased risk of oral cancer, whereas it was 32-fold in women. Thus it is possible that women have a greater susceptibility to oral tissue damage (Balaram *et al*., 2002).

Using SLT for a longer duration increases the oral cancer risk in Bangladesh. The present study findings show that 20 or less chew-years were associated with a six-fold increased risk of oral cancer, which escalates to nearly 26-fold for over 40 chew-years and this risk is higher among women. This finding is in line with the previous studies. The case-control study conducted by Khan *et al.,* (2017) found that a 28-fold increased risk of oral cancer for 20 pack-years of Naswar use. However, a case-control study from India reported a much lower risk. The study conducted by Gupta *et al*., (2017) reported that using SLT for 40 years or more resulted in an 11-fold increased risk of oral cancer. The type of SLT used in different countries and their variance in toxicity is likely to have contributed to this difference (NCI and CDC, 2014).

We found that, overall, 61% of oral cancer cases in Bangladesh are attributable to SLT use. The impact of SLT chewing was higher in women (76%) than men (41%). Up to 72% of oral cancer cases in men were associated with exposure to dual use of smoking and SLT use. Based on these estimates, it can be suggested that the high prevalence of SLT use amongst women and the dual use of smoking and SLT in men largely explains the incidences of oral cancer in Bangladesh. This suggests a high percentage of oral cancer cases in Bangladesh could be prevented if the SLT habit was addressed. These findings are comparable with previous studies conducted in India and Pakistan. Dikshit and Kanhere (2000) reported that 66% of oral cancer cases in India are attributable to SLT use alone. Previous studies carried out in India, which showed that the population attributable risk was higher among women and exceeded 80%, are in agreement with our study. However, contrary to our study, previous studies from Pakistan showed that men had the higher attributable risk of oral cancer from SLT use (68%) compared to women (38%) (Khan *et al.*, 2017). It is likely the type of SLT used in Pakistan will have contributed to this higher attributable fraction found amongst Pakistani men. Khan *et al.*, (2017) looked at the population attributable risk of oral cancer for 'Naswar' use, which is commonly used by men in Pakistan (Sinha *et al.,* 2017).

5.2.2 Role of other risk factors for oral cancer

In addition to SLT use, the present case-control study examined the risk of oral cancer from tobacco smoking, alcohol drinking, oral health practices, family history of cancer and BMI (Body Mass Index). We found that, overall, smoking amongst men increased the oral cancer risk. For the present study, cigarette smoking was not significantly associated with the oral cancer risk. Similar findings were reported in earlier studies carried out in India (Balaram *et al.,* 2003; Znaor *et al.*, 2003; Madani *et al.,* 2012*)*. However, in the present study, bidi smoking emerged as an independent risk factor for oral cancer in men. As mentioned in the literature review, bidi is an indigenous form of smoking, widely smoked in the South Asian subcontinent (Vyas *et al.,* 2018). Bidi is believed to have a higher level of nicotine and carcinogens (Rahman and Fukui, 2000). The finding of the bidi smoking in the present study was OR= 2.66, CI: (1.41-5.02) and is in line with previous studies and the odds ratio ranged from (OR: 2.6-3.1) (Balaram *et al.,* 2003; Muwonge *et al.*, 2008; Rahman *et al.*, 2003; Znaor *et al.,* 2003). There are several reasons that could explain this discrepancy. Firstly, the mean consumption of cigarette smoking did not differ significantly between the cases and controls. Perhaps we did not observe an association between cigarettes and oral cancer risk for this reason. Secondly, the overall toxicity is likely to be higher in bidi smoking compared to cigarettes (Rahman and Fukui, 2000). Thirdly, bidi is wrapped with tendu leaf, which is less porous than traditional cigarettes and has poor combustibility, which results in users inhaling a higher percentage of nicotine, tar and carbon monoxide. Bidi smokers tend to use more chewing tobacco and betel quid than cigarette smokers, which could also be another contributing factor (Rahman *et al.,* 2003). As a cheaper alternative to the cigarette, bidi is smoked widely by those from a lower socio-economic background and more frequently than cigarettes, which can contribute to oral cancer risk. In the present study, bidi smokers smoked more frequently than cigarette smokers did.

A novel finding of the present study was the increased risk of oral cancer among SLT users with poor oral hygiene (frequency of cleaning and the instrument used to clean teeth) compared to non-SLT users with poor oral hygiene. Amongst ever SLT users, using fingers and sticks to clean the teeth increased the oral cancer risk significantly compared to cleaning with a toothbrush. Also, less frequent teeth cleaning increased the oral cancer risk amongst SLT users. These findings are in line with the previous case-control study conducted by Gupta *et al.,* (2017), which found that the risk of oral cancer development in those who clean their teeth once a day or not at all was two-fold [OR:2.16 (95%CI: 1.18–3.93)] when the reference group was those that cleaned twice daily or more. Also, the oral cancer risk increased significantly for those who used fingers or a stick to clean their teeth OR: 1.29 (95%CI: 0.79–2.09). More frequent cleaning of the teeth has a preventive effect against mouth cancer, as was seen amongst the study subjects who had never had a tobacco and alcohol habit (Chan *et al*., 2017). Dental plaque removal through tooth brushing is likely to have a protective effect against oral cancer (Zeng *et al*., 2015). Dental plaque is known to be a reservoir of pathogens, produces nitrosamine and contributes to inflammation, which is a key component for the breakdown of normal cell growth and the initiation of carcinogenesis. Regular tooth brushing can remove both dental plaque and the toxic residues of tobacco and can therefore prevent or delay oral carcinogenesis (Gupta *et al.*, 2017).

The stratified analysis also showed that regular visits to the dentist reduce the oral cancer risk for non-SLT users. This confirms the similar findings of previous studies conducted by Chang, *et al.*, (2013), Ahrens, *et al.*, (2014), and Kawakita, *et al.*, (2017). This significant association between regular dental visits and oral cancer risk among non-SLT users may be an indication of better dental care habits. Also, regular dental visits allow the dentist to look for pre-malignant lesions and treat them. Then again, those who go to the dentist regularly may come from a higher socio-economic background, which was previously identified as an indicator of better health overall (Park *et al.,* 2016).

In this study, we found that leanness was associated with an increased risk of oral cancer. A similar proposition was made in earlier case-control studies (Kreimer *et al.*, 2006; Radoi *et al.,* 2013). The exact biological mechanism responsible for this association between BMI and oral cancer is still unknown, although there are two possible explanations for the association between leanness and oral cancer. Firstly, undiagnosed cancer lesions in the oral cavity may cause dysphagia or suppress taste and appetite, which could lead to a reduction of overall calorie intake and weight loss (Gaudet *et al.,* 2010). Another explanation is that BQ – the commonly used SLT in the present study – allegedly moderates the metabolic signals that control the appetite, resulting in suppressed hunger and an increased risk of malnutrition, and thus lowering BMI (Javed, *et al.,* 2010).

5.3 Strengths and limitations of the study

5.3.1 Key strengths and limitations of the cross-sectional survey

The cross-sectional survey has several key strengths and makes important contributions to adolescent SLT use in Bangladesh. To the best of the author's knowledge, this is the first study in the rural area of Bangladesh to exclusively look at adolescent SLT use and the factors that contribute to its current use. The findings of the present study will provide valuable insights for key stakeholders who aim to develop or implement policies and interventions that can prevent adolescent SLT use. We used a validated questionnaire from the WHO's GYTS (Global Youth Tobacco Survey), which enabled our findings to be compared with other similar studies in this field.

The generalisability of the present study is only limited to school-going adolescents. It is highly likely, with the high school dropout rate in rural Bangladesh being as high as nearly 40% for secondary schools (Sarkar, Wu, and Hossain, 2019), that the present study's findings may not be representative of school dropout adolescents. There is a great difference between the tobacco use status of school-going adolescents and school dropout students. Previous literature has suggested that school dropouts, or those who never been to school, are more likely to use tobacco, as they are not guided by school-based intervention and the supervision of teachers (Adebiyi *et al.,* 2010). Some studies have suggested that the tobacco prevalence of school dropout students is as high as over 50% (Desai *et al.,* 2019).

The school survey was based on self-reported data; therefore, the data collected may be subjective. There is the possibility that tobacco use was over or under-reported. Thus, a social desirability bias may have been introduced, as adolescents are less likely to report socially undesirable behaviours, such as tobacco use. However, a study conducted by Post *et al.,* (2005) among Swedish adolescents on smoking and SLT behaviour confirmed the validity of adolescents' self-reported tobacco use. In addition, a study conducted by Valladolid-López *et al.,* (2015) stated that self-reported smoking in the past 30 days, which is used as a tobacco behaviour measure in the GYTS (Global Youth Tobacco Survey), is a valid and stable indicator of current tobacco use behaviour. Moreover, ensuring anonymity and confidentiality enhanced the validity of the self-reported data. Also, the social acceptability of SLT use in Bangladeshi culture has lessened the effect of social desirability bias.

The cross-sectional design of the current study did not allow causal inferences between SLT use and other descriptive measures of interest. Longitudinal data would require the temporal relationships between the variables to be established. Consequently, establishing a cause-and-effect relationship in tobacco research would require a long-term follow-up study. Due to limited resources, only adolescents in two rural schools were included in this study. Therefore, it can be argued that the findings herein reported are not necessarily representative of the entire target population. Therefore, the generalisability of the study findings are limited.

The present school survey did not include information about parental SLT use. Though the results of previous studies showed that exposure to parental SLT use was a strong predictor of adolescent SLT use (Agaku *et al.*, 2013; Hussain, Zaheer and

Shafique, 2013; Bhaskar *et al.,* 2016), the study failed to include this information. As mentioned previously, the data collection tool for the study was adopted from the smokeless tobacco module of GYTS Version 1.0. It is similar to the GYTS questionnaire, although the questionnaire was designed to collect detailed information about smoked tobacco rather than exclusively look at SLT use.

5.3.2 Key strengths and limitations of the hospital-based case-control study

A hospital-based case-control study was carried out to determine the association between SLT use and oral cancer among Bangladeshi adults. A prospective cohort study would be the ideal way to establish the epidemiological associations between possible risk factors and disease (Gerstman, 2013), as mentioned in the methodology, but this is sometimes not feasible, especially when the outcome measure is as rare as oral cancer. Therefore, case-control studies are the most feasible method of understanding the risk factors. However, due to their retrospective nature, case-control studies are susceptible to different types of biases. This subsection will provide an overview of the key strengths and limitations of the case-control study, which is important for the correct interpretation of the present study's findings.

Strengths

For this study, we have only included histologically confirmed incidences of oral cancer cases. Recruiting histologically confirmed cases is considered to be gold standard practice and ensured the study's higher validity by minimising the chance of selection bias by recruiting only incidence cases. We have also minimised the chance of recall bias, thus ensuring a more accurate assessment of exposure of interest, compared to prevalent cases. Moreover, using the life grid during the interview helped to recall the past exposure accurately, and thus minimised the chance of recall bias.

We also recorded factors that influenced the participation and non-participation of cases and controls, which enabled us to understand whether these factors could significantly affect the findings. There was a high response rate for the study, which allowed the comparability of baseline demographic data and risk factors of participants and non-participants and claim against bias availability for the study. Non-respondents showed both comparable age and marital status, like the respondents, and current SLT use and regular smoking status among non-participant and participant cases were also similar. Moreover, current SLT use status among the controls was comparable to Bangladesh's national SLT prevalence, thus the evidence was representative of the source population.

Interviews were carried out with those with cases prior to disclosing the biopsy result to the patients. This strategy may have avoided the differential recall of exposure among cases and controls. In addition, as the interviewer did not know the case or control status of the interviewee, it reduced the chance of interviewer bias. Also, to avoid interviewer bias, efforts were taken to standardise the interview technique and the format of the interview questionnaire. As well as this, an identification number was used to minimise the interviewer's awareness of the case or control status of the interviewee.

In a case-control study, the selection of an appropriate control is vital to avoid selection bias. The controls should be comparable to cases in respect to the biases of hospitalisation and the choice of hospital. To ensure controls represented the distribution of the exposure in the study population, controls were selected from the same hospital as cases, which produced more confidence in the validity of the study findings. Recruiting controls from the same hospital also ensured there was comparable accuracy of information between cases. In addition, controls were selected from several disease sources whose risk factors were not related to exposure of interest, which allowed us to detect an effected estimate that was closer to the true effect.

For the present case-control study, every step was taken to ensure the minimisation of the confounder effects. During the design phase, age and gender were identified as potential confounders, therefore cases and controls were age and gender-matched to eliminate the confounding effects. Additionally, during multivariate analysis, odds ratios were adjusted for the matching factors to eliminate the effects of confounders, thus providing a higher validity of the study's findings.

Limitations

The case-control study design is an efficient method to study rare outcomes. However, there are important limitations inherent to this design (Melamed and Robinson, 2019). Though every effort was made to reduce study error, the study was susceptible to several types of biases, inherent to the case-control study design. One of the most cited limitations of the case-control study design is the potential for recall bias (Tenny and Hoffman, 2020). The recall bias in the case-control study is the increased likelihood of cases being recalled and reported more often than the controls. Although several efforts were made to address this issue, the chance of recall bias occurring cannot be ruled out.

Since this is a hospital-based case-control study, oral cancer cases may not be representative of the base population from which they came from. As the study hospital was a tertiary-level dental hospital and deals with only patients with dental problems, the possibility of selection bias cannot be ruled out. Moreover, it is difficult to measure the direction of bias, therefore, estimated oral cancer risk may possibly be overestimated or underestimated.

Another possible limitation of the current study was that we used hospital controls. As previous studies suggested, using population-based controls is the better fit for a hospital-based case-control study (Neupane, *et al.*, 2010). A general concern with the hospital controls is that it may not represent the study base, therefore it may introduce selection bias. One of the key requisites for the control group was that it should reflect the population from where the cases would arise. Being a tertiary-level dental hospital, only hospital patients were referred to in Bangladesh, therefore it was hard to define the exact catchment area of the hospital. Thus, recruiting hospital controls was the only viable option. Moreover, recruiting population controls would require more resources and be time-consuming.

One possible disadvantage of recruiting hospital control is that the risk factor for the study disease may also be the risk factor for the disease condition of the control, which is the cause of the control's hospitalisation. This may result in an underestimate of the strength of the association between exposure of interest and the outcome. Therefore, there may be a bias in favour of the risk factor in the analysis that compare oral cancer cases and controls. It would be difficult to detect any relationship between the exposure of interest and outcome, as we may have selected a control group who has a greater than expected prevalence of exposure of interest than exist in the general population. To prevent this situation, we tried to choose controls from a range of conditions, exempting any disease that is related to the exposure of interest (Woodward, 2014, p. 224). However, that may lead to excluded people who use SLT (and don't have oral cancer) from controls. Nevertheless, the SLT incidence of our control group was 26.3% and the national prevalence of SLT was 27.2% (WHO, 2017). Similarly, for the overall smoking incidence of our control group was 15.4% and the national smoking prevalence of Bangladesh was 18.0%, which demonstrates a good representation of the general population (WHO, 2017).

One of the potential limitations of the case-control study was interviewer bias, though several efforts were taken to address this issue. The aim was to make sure that the interviewer was not aware of the case-control status of the participants. The presence of oral cancer lesions was visible to the naked eye in several instances; therefore, the likelihood of the interviewer bias cannot be ruled out.

Like other observational studies, the association measured in the case-control study may or may not represent the causal relationship (Melamed and Robinson, 2019). Similar to the cohort study, the odds ratios in this study were adjusted for confounding factors. However, some important confounders may be unknown for rare outcomes like oral cancer. Some of the risk estimates of the current study had a considerably large confidence interval, which indicated a low level of precision of the odds ratio or potential bias in this estimate. Even with the unmeasured confounders, the high magnitude of the odds ratio suggests that a causal relationship between SLT and oral cancer amongst Bangladeshi adults cannot be ruled out.

5.4 Implications and Recommendation

5.4.1 Public health implications

The findings of the present studies have several public health implications. The results of the school survey indicated that SLT use amongst rural Bangladeshi adolescents was relatively lower than in other neighbouring countries like India, Pakistan and Myanmar. However, one of the original contributions of the present study that it identified was the key predictors of SLT use in rural Bangladeshi adolescents. Such information is expected to steer future interventions that aim to reduce SLT prevalence among the rural population. The present study found that self-efficacy, perceived barrier, perceived benefits, perceived severity and older age are the key predictors, which is consistent with the theories of risky behaviour and earlier studies. Interventions that address key constructs such as self-efficacy may increase the ability of adolescents to quit SLT or even prevent initiation. Moreover, incorporating self-efficacy as a cognitive behavioural intervention in several forms of tobacco use and nicotine dependency has proved successful. The anti-SLT programme should aim to decrease the perceptions that SLT use is beneficial. For example, SLT cessation intervention should focus on offsetting the sources of the message that dictate that SLT use is beneficial, such as movies, social media and other media. Generally, perceived severity serves as a good predictor of behaviour, and previous evidence has suggested that adolescent conceptualise potential SLT use related harm to include multiple health and non-health related consequences. Therefore, both health and non-health consequences could be crucial components of adolescent anti-SLT communication efforts.

While considering other demographic, environmental and personal factors of adolescent SLT use, the survey found that adolescents aged as early as seven years old or younger were using SLT, which is a public health concern. From public health perspectives, age of onset is important, as there is considerable evidence that age of initiation is linked to a higher level of nicotine dependence, with previous studies showing that early initiation of tobacco is strongly associated with greater nicotine dependence in both younger and older adulthood (US Department of Health Services, 2012). This consistent dose-response gradient indicated that the younger the age of SLT onset, the greater the degree of nicotine dependency. Early onset of SLT use is also associated with adverse health effects and a higher risk of transition to smoking. In addition, present case-control study results found that the average age of SLT onset was 23. This finding highlights the necessity for preventive efforts to focus on younger adolescents in rural areas of Bangladesh.

The adolescent cross-sectional survey highlights the influence of the social environment on adolescent SLT use and the importance of both social and commercial access to SLT products. The present cross-sectional survey findings showed that social sources, such as friends and family members, are the most common sources of SLT for adolescents. It is beyond the scope of the present study to determine why social sources turned out to be the main source, but this finding suggests that social sources need to be addressed in adolescent SLT prevention strategies. This finding also highlights the unique challenge faced by rural Bangladeshi adolescent in relation to the parental source. SLT use in Bangladesh is regarded as a common social activity and is shared between friends, relatives, and family members. In Bangladesh, SLT use has been a part of social gatherings and offered in local festivals, weddings, and other celebrations, rather than regarded as detrimental behaviour. Parents offer SLT to adolescents and regard this as a very normal thing to do. Misconceptions about the benefits and harmlessness of SLT use, combined with low awareness of the risk associated with SLT use, have contributed towards these social practices.

Commercial sources have continued to be an important source of SLT to rural Bangladeshi adolescents. The preliminary evidence supports the importance of commercial restrictions and their value in lowering adolescent tobacco use (Chatterjee *et al.,* 2016; Mistry *et al.,* 2018;). The present school survey indicated that nearly 90% of the current SLT users were able to buy SLT from commercial stores. Restricting commercial access to SLT by adolescents is a supply-side strategy and it represents a demand reduction approach to preventing SLT use. According to TCA (the Tobacco Control Act) 2013, the buying and selling of SLT to and by minors are prohibited in Bangladesh. The act was passed in 2013 and went live in 2015. The field data for the survey was collected in 2015; therefore, the efficiency of the new law is yet to be evaluated. However, recent studies from Bangladesh have already reported a poor implementation of this law and stated there is a lack of awareness and ignorance of the TCA (Alam, 2018). Adolescence is considered to be one of the most vulnerable age groups for tobacco uptake and is therefore one of the primary targets of tobacco control policies and interventions (Khan, 2016).

One of the key provisions of WHO FCTC article 14 was that government should provide tobacco cessation interventions for those who wish to quit tobacco (Nilan *et al.*, 2017). The present school survey showed the majority of users wanted to quit SLT, but professional support was not available. Our findings demonstrate the urgent need for an SLT cessation campaign. More work is needed to increase the capacity to promote SLT cessation among adolescents. However, planning cessation intervention is challenging, as Bangladeshi adolescents face the double burden of both tobacco smoking and SLT.

The adolescent cross-sectional survey findings showed that, despite adolescents having an overall good knowledge, misconceptions about the relative harm it causes compared to smoking and a poor understanding of SLT content was prevalent. This finding has implications for how authorities can communicate about the risk of SLT products use. Risk communication campaigns are effective when studies identify the intended audiences' overall understanding of the issue. A lower perception of harm from all tobacco products is associated with SLT use, and this indicates the need to change adolescents' perception about the dangers of all tobacco products and denormalise tobacco use through evidence-based interventions. Moreover, the present study findings suggest that it may be effective to message adolescents about the constituents of SLT products and the relative harm they cause, which is unfamiliar to them. Hence, there is a clear need to expand anti-tobacco messaging campaigns to demonstrate the risk associated with all forms of tobacco use and not solely focus on smoked tobacco.

The key findings of the present hospital-based case-control study indicate that the use of SLT is associated with a higher risk of oral cancer among Bangladeshi adults and an independent risk factor for oral cancer. This is the first epidemiological study of its kind that has looked at the risk of oral cancer from SLT use in Bangladesh. This local evidence was necessary to understand the risk of oral cancer from the type of SLT used in Bangladesh, as the contents of SLT products varied substantially from country to country. This variance in the contents of SLT products is likely to be responsible for the difference in oral cancer risk between developed and developing countries. The risk of oral cancer increases with the longer duration of SLT use. This finding explains why SLT chewing emerged as a stronger risk factor than smoking. With SLT, there is direct exposure to the mouth while the tobacco is being chewed for a long period of time. Whereas tobacco smoking involves inhaling smoke, which may lead to less contact with the mouth and more contact with the throat and lung than SLT. Given the various types of SLT used in Bangladesh and its popularity, there is an urgent need for the public to be made aware of the fact that SLT use increases oral cancer risk significantly. The present study findings showed an estimated 61% of oral cancer cases can be prevented in Bangladesh if SLT use can be eliminated.

The present case-control study findings indicate that Bangladeshi women have a higher risk of developing oral cancer from SLT use compared to men. Oral cancer is the fifth leading cause of death for Bangladeshi women (International Agency for

Research in Cancer, 2018). Moreover, Bangladesh is the only country in South Asia where the prevalence of SLT is higher among women than it is among men. Bangladesh has an estimated population of 167 million, of which 81.3 million are women. Women play a key role in the economic development of Bangladesh. Home-based working women contributed an estimated US$2.59 billion to the total GDP (Gross domestic product) (Efroymson, Buddhadeb, and Ruma, 2007). There are four million garment workers in Bangladesh and 70% of these workers are women (Masum *et al.,* 2017); therefore, it is in the country's national interest that women are protected from SLT-related harm. Our estimation shows that eliminating SLT use amongst women would prevent roughly 76% of oral cancer cases among Bangladeshi women. Therefore, a tobacco cessation strategy is required that must address women's SLT use. However, little is known about gender differences in attempts to quit SLT use. Given the misconceptions surrounding the harm caused by SLT use, cultural stigma and a lack of awareness regarding the addictive nature of the SLT products, there is an urgent need for gender-specific interventions targeting women.

Amongst men, the highest risk of oral cancer was observed for dual users (both smoking tobacco and SLT). The present study's findings demonstrate that tobacco control policies based on the control of a single risk factor targeting Bangladeshi men are fated to fail in the long-term. Therefore, a comprehensive tobacco control programme is needed that will deal with both SLT and smoked tobacco on an equal footing, which is also critical for the effectiveness of SLT control regulation. As with the stricter policy for smoked tobacco control, there is the possibility that tobacco users will switch to cheaper alternatives.

The present case-control study revealed that BQ, with and without tobacco, increases the risk of oral cancer substantially, as well as independent risk factors. Nevertheless, the risk is lower when BQ is chewed without tobacco. This finding supports previous study findings that the areca nut – one of the major components of BQ – is likely to be the main reason for the carcinogenicity of chewing BQ without tobacco. There is a need in Bangladesh for aggressive campaigns against BQ chewing, both with and without tobacco, alongside campaigns for smoking tobacco. In Bangladesh, BQ without tobacco is not considered to be as dangerous and it is believed that the betel juice is good for digestion, so it is often indulged by women and adolescents. However, BQ that has no tobacco should not be regarded as a safer alternative to BQ with tobacco. The current study findings stress it is important that the WHO FCTC places extra attention on SLT, including BQ. This initiative is likely to inform the appropriate measure that is required to prevent oral cancer in Bangladesh and other Asian countries.

Regarding the other oral cancer risk factors, the present study's results clearly indicate that bidi smoking increases oral cancer risk amongst men. It is essential that this information is incorporated into overall smoking prevention and cessation efforts and special focus should be given to poorer urban and rural areas where bidi smoking is widespread (Warnakulasuriya, 2005). There is a widespread misconception that bidi smoking is less harmful than cigarette smoking (Rahman *et al.,* 2003). An awareness campaign should include messages that rectify these misconceptions. Bidi packets should follow the other tobacco products in having legally-required health hazard warnings – and nicotine and tar levels – on the packaging. In addition, the present study's findings indicate that poor oral hygiene is associated with an increased risk of oral cancer. Oral cancer prevention strategies may want to consider promoting good oral hygiene practices and regular visits to the dentist. In Bangladesh, national campaigns informing the general population about the beneficial effects of twice-daily tooth brushing and the appropriate method are essential to prevent oral cancer. Additionally, the campaign should promote the message that regular visits to the dentist are essential to minimise the risk of oral cancer.

5.4.2 Recommendation for public health actions

Based on the survey findings, anti-SLT interventions, addressing several key constructs from the Health Belief Model (HBM) and Social Cognitive Theory (SCT) can be effective in preventing adolescent SLT use. In addition, efforts should be made to increase adolescent awareness of the addictive nature of SLT. This may include public health education that targets adolescents with regards to the potential harm and addictiveness of SLT in order to reduce its appeal among adolescents.

To ensure adolescents do not take up this habit at a young age, the national anti-SLT campaigns in Bangladesh should extend their coverage to primary schools (5th Grade) rather than focusing on high schools (6th grade and above). As Bangladeshi adolescents are facing the double burden of smoking and SLT, a tobacco cessation programme that addresses multiple forms of tobacco use would be appropriate for them.

To restrict the access and availability of SLT products to Bangladeshi adolescents both commercial and social sources need to be addressed. To ensure that the selling or buying of SLT by minors is banned, a comprehensive policy formulation, effective intervention and proper enforcement of the law are required. In addition, to prevent the social source of SLT products for adolescents, policy interventions should target peer networks, with regulatory and messaging campaigns. Such regulatory initiatives and campaigns should aim to create a perception that tobacco is difficult to obtain and consume, which would reduce the amount of tobacco experimentation and the opportunity for social exchange. Furthermore, to address the parental source of SLT, interventions are needed to ensure that parents understand the danger of using SLT and stop offering it to adolescents. In addition, parents who use SLT should be encouraged to quit.

Given the risk of oral cancer that is associated with SLT use among Bangladeshi adults, tobacco control measures in Bangladesh should address both smoked tobacco and SLT and include legislative and administrative measures that address several issues such as advertising, trade between countries, and the low tax rate on SLT products. In relation to the taxation of tobacco products, Bangladesh should focus on building its capacity to administer similar taxes on all types of tobacco – including SLT products – which will prevent switching to cheaper options or dual use.

To reduce the excess risk of oral cancer among Bangladeshi women, the national tobacco control strategy should address women's SLT use and prevent the distribution and sale of unregulated SLT products (such as 'Sadapata'), which is mostly used by Bangladeshi women. Overall, SLT cessation strategies should be combined with inclusive tobacco control legislation and all of these approaches should consider gender-specific efforts and other factors that can affect SLT use in Bangladesh and other low-middle-income countries.

The present study findings emphasise the need for public health interventions targeted at both SLT use and smoking. The general public should be aware of the high risk of oral cancer associated with BQ chewing, with or without tobacco, as well as bidi smoking. Given the relatively poor survival rates of oral cancer patients, prevention and cessation of both forms of tobacco use remain as key elements in effectively preventing and controlling oral cancer.

5.4.3 Recommendations for future research

The cross-sectional study has added knowledge to the limited literature that exists on SLT use among adolescents in Bangladesh. To the best of the author's knowledge, this is the first study of its kind to look exclusively at adolescent SLT use and its associated factors in Bangladesh. Future studies should consider incorporating both qualitative and quantitative methods by expanding the scope of the study and assessing a wider range of data. Future studies should also consider conducting research in both urban and rural settings to determine the disparity that exists in the prevalence of adolescent SLT use in different geographical areas with different socio-economic status. There is limited literature that compares SLT usage among adolescents in urban and rural schools in Bangladesh.

Despite the relatively low prevalence of SLT use amongst Bangladeshi adolescents, it is essential to continue monitoring SLT use. This should be complemented by the monitoring of this age group's exposure to tobacco promotion and access to SLT, as it is essential for an understanding of SLT use trends and for appropriate evaluation of tobacco control efforts. Future studies should also consider conducting a prospective study to follow adolescents over time, as this could enable the causal relationship between descriptive factors and SLT use to be established. Following adolescents over time could help researchers to determine whether SLT use leads to the smoking of cigarettes or the regular use of SLT in Bangladesh.

Since social connections were the predominant source of SLT for the Bangladeshi adolescents, a further longitudinal study should be carried out to understand the impact of banning the sale of SLT products, as well as the effect that this would have on sourcing SLT products through social connections. In addition, extensive studies need to be carried out to find out how to make SLT less accessible and available to adolescents from social sources.

The case-control study findings contributed to causal knowledge of the oral cancer risk posed by SLT use in Bangladesh. It also supported previous study findings on other behavioural factors – such as bidi smoking and oral hygiene factors. Findings of the present case-control study underline both the need for and importance of further study with a larger sample size, incorporating methodologies, such as the life course approach and other biological and genetic factors. These may help to create a better understanding of the aetiology of oral cancer amongst Bangladeshi adults.

The present case-control study found there is a strong association between SLT use and the risk of oral cancer after controlling for other measurers (age, gender, educational status, employment status, smoking and BMI). Future case-control studies should consider other mediators, such as Human Papilloma Virus (HPV) and diet. Nitrosamine is recognised as the most potent of carcinogens in SLT products. The combined carcinogenic effect of both SLT products with high-risk HPV has been previously indicated. However, this association has yet to be elucidated as some studies have suggested an inversely proportional association between high-risk HPV DNA detection in cancer specimens and tobacco consumption, which warrants further research to characterise this relationship (Sand *et al.*, 2014).

The positive association between SLT product uses in Bangladesh and the risk of oral cancer also warrants future research to look at the risk of pre-malignant lesions from SLT use in Bangladesh. The preliminary plan for the present study was to include oral leukoplakia and mouth cancer patients. However, during the six-month period, we did not observe a single oral pre-cancerous lesion case in the hospital. Thus, future studies in Bangladesh should aim to recruit oral pre-malignant lesion cases from a population source other than hospitals. However, recruiting cases from population sources in Bangladesh requires additional resources and is a time-consuming process.

The present study's findings showed both betel quid – with and without tobacco – were associated with the risk of oral cancer. Future studies should consider a product-specific association that would enable an effective policy decision and refute claims SLT reduces harm and is an alternative to quitting smoking tobacco. To do this, future studies should link the contents and biomarkers of that specific SLT product with oral cancer. However, it will be extremely challenging to establish these links as the content of SLT products varies from region to region, even within the country. Custom-made and cottage industry SLT products have little or no standardisation. In addition, future studies should consider the health effects of the other ingredients that are consumed with the SLT products, such as slaked lime, betel nut, catechu (also locally known as 'khair') and other flavouring agents. For the present study, we tried to capture people who chewed betel nut exclusively. However, there were only a few respondents that consumed betel nut alone, but a future study with a larger sample size should be able to capture this information.

For the present case-control study, more than 12% (41) of the younger patients under 40 years old had been diagnosed with oral cancer. Previous studies suggested an absence of traditional risk factors amongst younger patients (Llewellyn *et al.,* 2004). Additionally, the time span for traditional carcinogens, such as smoking, smokeless tobacco or alcohol drinking, to exert an adverse effect among these younger patients is comparatively short compared to older patients, thus, suggesting that oral cancer among younger patients may be distinct from oral cancer among older patients and may not be contributing to the traditional risk factors (Llewellyn *et al.,* 2001). Consequently, future research should examine other environmental carcinogens and the previous history of viral infection among this age group.

Our study findings indicated that a low BMI was associated with increased oral cancer risk. The exact biological mechanism of the association between BMI and oral cancer is still unknown. A prospective study is needed to explore this association amongst Bangladeshi adults. Moreover, the present study findings warrant future studies in Bangladesh that consider BMI changes in adulthood, such as the difference in BMI 2 years before the interview and BMI during the interview. This would allow us to understand the true effects of BMI on oral cancer risk amongst the selected population. However, recording the height and weight 2 years prior to the interview would be challenging, as it was the first time that many of the present study's participants had been on the weighing scales and some had never known their previous weight, thus there is a high chance of misclassification bias.

5.5 Conclusions

SLT use is a major public health burden. Considering the scale and complexity of SLT use-related problems, such as trend and current use, industry marketing, effective legislation, and a lack of evidence-based interventions, this major public health burden warrants greater consideration and action. The prevalence of SLT and the amount of oral cancer-related deaths in Bangladesh is among the highest in the world. Despite that the epidemiological evidence related to SLT use and its association with deadly diseases like oral cancer is limited or non-existent. Therefore, the aim of this PhD research is to fill this current knowledge gap by looking at SLT use among Bangladeshi adolescents, as well as the factors associated with current use, and to determine what the association is between SLT use and the risk of oral cancer among Bangladeshi adults. Thus, this evidence will inform interventions that will be tailored to the prevention and cessation of SLT use in Bangladesh. A school-based survey and a hospital-based case-control study were conducted to attain the study objectives.

Findings from this adolescent cross-sectional survey indicate that SLT incidence amongst rural Bangladeshi adolescents is low compared to other neighbouring countries. However, early exposure to SLT is a public health concern. Boys were the predominant users, which follows the same trend that is found in other South Asian countries. Most adolescents sourced their SLT from social connections and the majority of current users are able to buy SLT products from stores without any restrictions, despite a government ban on selling SLT to minors. Another indication of poor implementation of current TCA is that many students did not notice any of the health warning signs. Professional help to quit SLT is non-existent in rural areas of Bangladesh. Overall, rural adolescents had a good knowledge of the adverse effects of SLT. However, there was a widely held misconception about the addictiveness of SLT and its relative harm compared to cigarettes. The key predictors of current SLT use include several constructs from the SCT (Social Cognitive Theory) and Health Belief Model (HBM) – namely, perceived benefit, perceived severity, self-efficacy, and the perceived barriers.

The result of the case-control study indicates there is a strong link between SLT use and oral cancer amongst Bangladeshi adults. It was found that women had a higher risk of developing oral cancer from SLT use. Amongst the men, dual users (SLT + Smoked tobacco) had the highest risk of developing oral cancer. The present case-control study findings showed that betel quid, with or without tobacco, are both strong and independent risk factors for oral cancer. The use of SLT showed a clear and strong dose-response relationship for frequency and the duration of use. The dose-response relationship was strongest among the women.

Overall, in line with the studies from other countries in the SEAR region, the present study confirmed that SLT use is a strong risk factor in the aetiology of oral cancer in Bangladesh, while smoking tobacco in combination with SLT may also have an important role among Bangladeshi men. Preventive efforts to encourage current chewers to quit SLT are likely to be the most effective way to reduce the current burden of oral cancer in Bangladesh.

References

Abbe, R., (1915) 'Cancer of the mouth', *The Laryngoscope*, 25(8).

Abdullah, A.S., Driezen, P., Ruthbah, U.H., Nargis, N., Quah, A.C.K. and Fong, G.T. (2014) 'Patterns and Predictors of Smokeless Tobacco Use among Adults in Bangladesh: Findings from the International Tobacco Control (ITC) Bangladesh Survey', *PLoS One,* 9(7), pp. e101934. doi: 10.1371/journal.pone.0101934.

Abroms, L., Simons-Morton, B., Haynie, D.L. and Chen, R. (2005) 'Psychosocial predictors of smoking trajectories during middle and high school', *Addiction,* 100(6), pp. 852-861. doi: 10.1111/j.1360-0443.2005.01090.x.

Adebiyi, A.O., Faseru, B., Sangowawa, A.O. and Owoaje, E.T. (2010) 'Tobacco use amongst out of school adolescents in a local government area in Nigeria', Substance abuse treatment, prevention and policy, 5(1), pp. 24. doi: 10.1186/1747-597X-5-24.

Adedigba, M.A., Aransiola, J., Arobieke, R.I., Adewole, O. and Oyelami, T. (2018) 'Between Traditions and Health: Beliefs and Perceptions of Health Effects of Smokeless Tobacco Among Selected Users in Nigeria', *Substance Use & Misuse,* 53(4), pp. 565. doi: 10.1080/10826084.2017.1349796.

Agaku, I.T. and Alpert, H.R. (2016) 'Trends in annual sales and current use of cigarettes, cigars, roll-your-own tobacco, pipes, and smokeless tobacco among US adults, 2002–2012', *Tobacco Control,* 25(4), pp. 451-457. doi: 10.1136/tobaccocontrol-2014-052125.

Agaku, I.T. and Ayo-Yusuf, O.A. (2014) 'The Effect of Exposure to Pro-Tobacco Advertising on Experimentation With Emerging Tobacco Products Among U.S. Adolescents', *Health Education & Behavior: The Official Publication of the Society for Public Health Education,* 41(3), pp. 275-280. doi: 10.1177/1090198113511817.

Agaku, I.T., Ayo-Yusuf, O.A., Vardavas, C.I. and Connolly, G. (2014) 'Predictors and Patterns of Cigarette and Smokeless Tobacco Use Among Adolescents in 32 Countries, 2007–2011', *Journal of Adolescent Health,* 54(1), pp. 47-53. doi: //0-dx.doi.org.brum.beds.ac.uk/10.1016/j.jadohealth.2013.07.037.

Agaku, I.T., Ayo-Yusuf, O.A., Vardavas, C.I., Alpert, H.R. and Connolly, G.N. (2013) 'Use of Conventional and Novel Smokeless Tobacco Products Among US Adolescents', *Pediatrics,* 132(3), pp. e578-e586. doi: 10.1542/peds.2013-0843.

Agbor, M.A., Azodo, C.C. and Tefouet, T. (2013) 'mokeless tobacco use, tooth loss and oral health issues among adults in Cameroon', *African Health Sciences*, 13(3), pp. 785-790. doi: 10.4314/ahs.v13i3.38.

Ahmed, H.G. (2013) 'Aetiology of oral cancer in the Sudan', *Journal of oral & maxillofacial research,* 4(2), pp. e3. doi: 10.5037/jomr.2013.4203.

Ahrens, W., Pohlabeln, H., Foraita, R., Nelis, M., Lagiou, P., Lagiou, A., Bouchardy, C., Slamova, A., Schejbalova, M., Merletti, F., Richiardi, L., Kjaerheim, K., Agudo, A., Castellsague, X., Macfarlane, T.V., Macfarlane, G.J., Lee, Y.A., Talamini, R., Barzan, L., Canova, C., Simonato, L., Thomson, P., McKinney, P.A., McMahon, A.D., Znaor, A., Healy, C.M., McCartan, B.E., Metspalu, A., Marron, M., Hashibe, M., Conway, D.I. and Brennan, P. (2014) 'Oral health, dental care and mouthwash associated with upper aerodigestive tract cancer risk in Europe: the ARCAGE study', *Oral Oncology,* 50(6), pp. 616-625. doi: 10.1016/j.oraloncology.2014.03.001.

Akers, R.L. and Lee, G. (1996) 'A Longitudinal Test of Social Learning Theory: Adolescent Smoking', *Journal of Drug Issues,* 26(2), pp. 317-343. doi: 10.1177/002204269602600203.

Akhter, M., Ali, L., Hassan, Z. and Khan, I. (2013) 'Association of Human Papilloma Virus Infection and Oral Squamous Cell Carcinoma in Bangladesh', *The Journal of Health, Population and Nutrition,* 31(1), pp. 65.

Akhter, R., Hassan, N.M.M., Aida, J., Takinami, S. and Morita, M. (2008) 'Relationship between betel quid additives and established periodontitis among Bangladeshi subjects' *Journal of clinical periodontology,* 35 (1), pp. 9.

Akther, F. (2011) *Tobacco cultivation and its impact on food production in Bangladesh.* Available at: ubinig.org/cpdf/21_53.pdf (Accessed: July 13, 2018)

Al Agili, D.E. and Park, H. (2013) 'Oral health status of male adolescent smokeless tobacco users in Saudi Arabia', *Eastern Mediterranean Health Journal*, 19(8), pp. 711.

Alam, R.M.D. (2018) *Smokeless Tobacco Use and Tobacco control In Bangladesh.* Available at: http://untobaccocontrol.org/kh/smokeless-tobacco/background-documents/ (Accessed: June 15, 2019).

Albar, M.A. (1994) 'Islamic teachings and cancer prevention', *Journal of family & community medicine,* 1(1), pp. 79.

Allen, L.N., Pullar, J., Wickramasinghe, K., Williams, J., Foster, C., Roberts, N., Mikkelsen, B., Varghese, C. and Townsend, N. (2017) 'Are WHO "best buys" for non-communicable diseases effective in low-income and lower-middle-income countries? A systematic review', *The Lancet Global Health,* 5, pp. S17. doi: 10.1016/S2214-109X(17)30124-9.

Almahdi, H.M., Ali, R.W., Nasir, E.F. and Astrom, A.N. (2017) 'Socio-cognitive correlates of intention to use Toombak: a cross-sectional study among students (13-16 years) in Khartoum State, Sudan', *BMC Public Health,* 18(1), pp. 1-9. doi: 10.1186/s12889-017-4606-z.

Alsanosy, R.M. (2014) 'Smokeless tobacco (shammah) in Saudi Arabia: a review of its pattern of use, prevalence, and potential role in oral cancer', *Asian Pac J Cancer Prev*. 2014;15(16):6477-83.

Alumran, A., Hou, X. and Hurst, C. (2012) 'Validity and reliability of instruments designed to measure factors influencing the overuse of antibiotics', Journal of infection and public health, 5(3), pp. 221-232. doi: 10.1016/j.jiph.2012.03.003.

Alves, J., Perelman, J., Soto-Rojas, V., Richter, M., Rimpelä, A., Loureiro, I., Federico, B., Kuipers, M.A.G., Kunst, A.E. and Lorant, V. (2017) 'The role of parental smoking on adolescent smoking and its social patterning: a cross-sectional survey in six European cities', *Journal of Public Health (Oxford, England),* 39(2), pp. 339-346. doi: 10.1093/pubmed/fdw040.

Amarasena, N., Ekanayaka, A.N.I., Herath, L. and Miyazaki, H. (2003) 'Association between smoking, betel chewing and gingival bleeding in rural Sri Lanka', *Journal of clinical periodontology,* 30(5), pp. 403-408. doi: 10.1034/j.1600-051X.2003.20010.x.

American Cancer Society (2014) Early Theories about Cancer Causes | American Cancer Society. Available at: https://www.cancer.org/cancer/cancer-basics/history-of-cancer/cancer-causes-theories-throughout-history.html (Accessed: May 18, 2020).

Amtha, R., Razak, I.A., Basuki, B., Roeslan, B.O., Gautama, W., Puwanto, D.J., Ghani, W.M.N. and Zain, R.B. (2014) 'Tobacco (kretek) smoking, betel quid chewing and risk of oral cancer in a selected Jakarta population', *Asian Pacific journal of cancer prevention : APJCP,* 15(20), pp. 8673-8678. doi: 10.7314/APJCP.2014.15.20.8673.

Anand, P S, Bansal, A, Dwivedi, S, Kamath, K P and Anil, S (2013) 'Comparison of periodontal destruction patterns among patients with and without the habit of smokeless tobacco use - A retrospective study', *Journal of periodontal research,* 48(5), pp. 623-631. doi: 10.1111/jre.12048.

Anantharaman, D., Marron, M., Lagiou, P., Samoli, E., Ahrens, W., Pohlabeln, H., Slamova, A., Schejbalova, M., Merletti, F., Richiardi, L., Kjaerheim, K., Castellsague, X., Agudo, A., Talamini, R., Barzan, L., Macfarlane, T.V., Tickle, M., Simonato, L., Canova, C., Conway, D.I., McKinney, P.A., Thomson, P., Znaor, A., Healy, C.M., McCartan, B.E., Hashibe, M., Brennan, P. and Macfarlane, G.J. (2011) 'Population attributable risk of tobacco and alcohol for upper aerodigestive tract cancer', *Oral Oncology,* 47(8), pp. 725-731. doi: 10.1016/j.oraloncology.2011.05.004.

Andersson, G. and Axèll, T. (1989) 'Clinical appearance of lesions associated with the use of loose and portion-bag packed Swedish moist snuff: a comparative study', *Journal of Oral Pathology & Medicine*, 18(1), pp. 2-7. doi: 10.1111/j.1600-0714.1989.tb00722.x..

Andre, K., Schraub, S., Mercier, M. and Bontemps, P. (1995) 'Role of alcohol and tobacco in the aetiology of head and neck cancer: A case-control study in the doubs region of France', *European Journal of Cancer. Part B: Oral Oncology,* 31(5), pp. 301-309. doi: 10.1016/0964-1955(95)00041-0.

Antunes, J.L.F., Toporcov, N.T., Biazevic, M.G.H., Boing, A.F., Scully, C. and Petti, S. (2013) 'Joint and Independent Effects of Alcohol Drinking and Tobacco Smoking on Oral Cancer: A Large Case-Control Study', *PLoS One,* 8(7), pp. e68132. doi: 10.1371/journal.pone.0068132.

Aryal, U.R., Petzold, M. and Krettek, A. (2013) 'Perceived risks and benefits of cigarette smoking among Nepalese adolescents: a population-based cross-sectional study', *BMC public health,* 13(1), pp. 187. doi: 10.1186/1471-2458-13-187.

Asthana, S., Labani, S., Kailash, U., Sinha, D.N. and Mehrotra, R. (2018) 'Association of Smokeless Tobacco Use and Oral Cancer: A Systematic Global Review and Meta-Analysis', *Nicotine & Tobacco Research,* doi: 10.1093/ntr/nty074.

Atari, D.O. (2014) 'Gender differences in the prevalence and determinants of tobacco use among school-aged adolescents (11-17 years) in Sudan and South Sudan', *The Pan African Medical Journal,* 18, pp. 118. doi: 10.11604/pamj.2014.18.118.3202.

Awan, K.H. and Patil, S. (2016) 'Association of Smokeless Tobacco with Oral Cancer - Evidence From the South Asian Studies: A Systematic Review', *Journal of the College of Physicians and Surgeons--Pakistan : JCPSP,* 26(9), pp. 775.

Axton, W.F. (2015) *Tobacco and Kentucky.* 1st edn. Lexington: The University Press of Kentucky.

Ayo-Yusuf, O.A., Swart, T.J.P. and Pickworth, W.B. (2004) 'Nicotine delivery capabilities of smokeless tobacco products and implications for control of tobacco dependence in South Africa', *Tobacco Control,* 13(2), pp. 186-189. doi: 10.1136/tc.2003.006601.

Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V., Scotti, L., Jenab, M., Turati, F., Pasquali, E., Pelucchi, C., Galeone, C., Bellocco, R., Negri, E., Corrao, G., Boffetta, P. and La Vecchia, C. (2015) 'Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis', *British journal of cancer*, 112(3), pp. 580-593. doi: 10.1038/bjc.2014.579.

Bakdash, A. (2017) 'Shammah (Smokeless Tobacco) and public health', *Asian Pacific Journal of Cancer Prevention,* 18(5), pp. 1183-1190. doi: 10.22034/APJCP.2017.18.5.1183.

Baker, R., Taylor, E., Essafi, S., Jarvis, J.D. and Odok, C. (2016) 'Engaging young people in the prevention of noncommunicable diseases', *Bulletin of the World Health Organisation,* 94(7), pp. 484. doi: 10.2471/BLT.16.179382.

Balaram, P., Sridhar, H., Rajkumar, T., Vaccarella, S., Herrero, R., Nandakumar, A., Ravichandran, K., Ramdas, K., Sankaranarayanan, R., Gajalakshmi, V., Muñoz, N. and Franceschi, S. (2002) 'Oral cancer in southern India: The influence of smoking, drinking, paan-chewing and oral hygiene', *International Journal of Cancer,* 98(3), pp. 440-445. doi: 10.1002/ijc.10200.

Ballantyne, G.H. (1988) 'Theories of carcinogenesis and their impact on surgical treatment of colorectal cancer. A historical review', *Diseases of the colon and rectum,* 31(7), pp. 513-517. doi: 10.1007/BF02553723.

Bandura, A. (1986) *Social foundations of thought and action.* 2nd edn. Englewood Cliffs, N.J: Prentice-Hall.

Bangladesh Bureau of Statistics (2017) Statistical Yearbook Bangladesh 2016. Dhaka: Ministry of Planning. Available at: www.bbs.gov.bd (Accessed: 19 May, 2018).

Barkat A Chowdhury A, Nargis N, Rahman M, Kumar P, Bashir S, Chaloupka F J (2012) *The Economics of Tobacco and Tobacco Taxation in Bangladesh. Paris:* Available at: https://www.tobaccofreekids.org/global.../the_economics_of_tobacco_and_tobacco_ta (Accessed: July 14 2017)

Belinsky, S.A., Foley, J.F., White, C.M., Anderson, M.W. and Maronpot, R.R. (1990) 'Dose-response relationship between O6-methylguanine formation in Clara cells and induction of pulmonary neoplasia in the rat by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone', *Cancer Research,* 50(12), pp. 3772-3780.

Bellatorre, A., Choi, K. and Bernat, D. (2015) 'The Influence of the Social Environment on Youth Smoking Status', *Preventive medicine,* 81, pp. 309-313. doi: 10.1016/j.ypmed.2015.09.017.

Benjamin, R.M. (2012) 'A New Surgeon General's Report: Preventing Tobacco Use Among Adolescents and Young Adults'. *Public Health Reports* (1974-), 127(4), pp. 360-361. doi: 10.1177/003335491212700402.

Bernaards, C.M., Twisk, J.W.R., Snel, J., Mechelen, W.V. and Kemper, H.C.G. (2001) 'Is calculating pack-years retrospectively a valid method to estimate life-time tobacco smoking? A comparison between prospectively calculated pack-years and retrospectively calculated pack-years', *Addiction,* 96(11), pp. 1653-1661. doi: 10.1046/j.1360-0443.2001.9611165311.x.

Berney, L.R. and Blane, D.B. (1997) 'Collecting retrospective data: Accuracy of recall after 50 years judged against historical records', *Social Science & Medicine,* 45(10), pp. 1519-1525. doi: 10.1016/S0277-9536(97)00088-9.

Bhaskar, R.K., Sah, M.N., Gaurav, K., Bhaskar, S.C., Singh, R., Yadav, M.K. and Ojha, S. (2016) 'Prevalence and correlates of tobacco use among adolescents in the schools of Kalaiya, Nepal: a cross-sectional questionnaire-based study', *Tobacco induced diseases,* 14, pp. 11. doi: 10.1186/s12971-016-0075-x.

Bhaskaran, K., Douglas, I., Forbes, H., dos-Santos-Silva, I., Leon, D.A. and Smeeth, L. (2014) 'Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults', *Lancet (London, England),* 384(9945), pp. 755-765. doi: 10.1016/S0140-6736(14)60892-8.

Bhuiyan, M., Ovi, F., Alam, M. and Hossain, D. (2015) *Fighting Tobacco Promotion in Bangladesh: A Framework for Implementing TAPS Ban in the Light of Tobacco*

Control Law. Available at: ecbangladesh.org/wp-content/uploads/2015/07/Tobacco-Framework_Eng-Final.pdf (Accessed: July 15, 2018).

Bile, K.M., Shaikh, J.A., Afridi, H.U.R. and Khan, Y. (2010) 'Smokeless tobacco use in Pakistan and its association with oropharyngeal cancer', *Eastern Mediterranean Health Journal,* 16, pp. S30.

Biswas, T., Pervin, S., Tanim, M.I.A., Niessen, L. and Islam, A. (2017) 'Bangladesh policy on prevention and control of non-communicable diseases: a policy analysis', *BMC public health,* 17(1), pp. 582-11. doi: 10.1186/s12889-017-4494-2.

Blane, D.B. (1996) 'Collecting retrospective data: Development of a reliable method and a pilot study of its use', *Social Science & Medicine,* 42(5), pp. 751-757. doi: 10.1016/0277-9536(95)00340-1.

Bleich, S.N., Koehlmoos, T.L.P., Rashid, M., Peters, D.H. and Anderson, G. (2010) 'Noncommunicable chronic disease in Bangladesh: Overview of existing programs and priorities going forward', *Health Policy*, 100(2), pp. 282-289. doi: 10.1016/j.healthpol.2010.09.004.

Blomgren, K.J., Sundström, A., Steineck, G. and Wiholm, B. (2006) 'Interviewer Variability: Quality Aspects in a Case: Control Study', *European Journal of Epidemiology,* 21(4), pp. 267-277. doi: 10.1007/s10654-006-0017-7.

Blot, W.J., McLaughlin, J.K., Winn, D.M., Austin, D.F., Greenberg, R.S., Preston-Martin, S., Bernstein, L., Schoenberg, J.B., Stemhagen, A. and Fraumeni, J.F., Jr (1988) 'Smoking and Drinking in Relation to Oral and Pharyngeal Cancer', *Cancer Research,* 48(11), pp. 3282-3287.

Boffetta, P., Aagnes, B., Weiderpass, E. and Andersen, A. (2005) 'Smokeless tobacco use and risk of cancer of the pancreas and other organs', *International Journal of Cancer,* 114(6), pp. 992-995. doi: 10.1002/ijc.20811.

Boffetta, P., Hecht, S., Gray, N., Gupta, P. and Straif, K. (2008) 'Smokeless tobacco and cancer', *The Lancet Oncology,* 9(7), pp. 667-675. doi: //dx.doi.org/10.1016/S1470-2045(08)70173-6.

Bongaarts, J. (2016) *Health in 2015: From MDGs, Millennium Development Goals, to SDGs, Sustainable Development Goals*, New York: Wiley Subscription Services, Inc.

Bosetti, C., Gallus, S., Trichopoulou, A., Talamini, R., Franceschi, S., Negri, E. and Vecchia, C.L. (2003) 'Influence of the Mediterranean Diet on the Risk of Cancers of the Upper Aerodigestive Tract', *Cancer Epidemiology Biomarkers & Prevention,* 12(10), pp. 1091.

Bouquot, J.E. and Meckstroth, R.L. (2009) 'Oral cancer in a tobacco-chewing US population—no apparent increased incidence or mortality', *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology,* 86(6), pp. 697-706. doi: 10.1016/S1079-2104(98)90207-4.

Braakhuis, B.J.M., Rietbergen, M.M., Buijze, M., Snijders, P.J.F., Bloemena, E., Brakenhoff, R.H. and Leemans, C.R. (2014) 'TP53 mutation and human papilloma virus status of oral squamous cell carcinomas in young adult patients', *Oral Diseases,* 20(6), pp. 602-608. doi: 10.1111/odi.12178.

Bragelmann, J., Dagogo-Jack, I., Dinali, M.E., Stricker, T., Brown, C.D., Zuo, Z., Khattri, A., Keck, M., McNerney, M.E., Longnecker, R., Bieging, K., Kocherginsky, M., Alexander, K., Salgia, R., Lingen, M.W., Vokes, E.E., White, K.P., Cohen, E.E.W. and Seiwert, T.Y. (2013) 'Oral cavity tumors in younger patients show a poor prognosis and do not contain viral RNA', *Oral Oncology,* 49(6), pp. 525-533. doi: 10.1016/j.oraloncology.2013.02.003.

Bravi, F., Bosetti, C., Filomeno, M., Levi, F., Garavello, W., Galimberti, S., Negri, E. and Vecchia, C.L. (2013) 'Foods, nutrients and the risk of oral and pharyngeal cancer', *British Journal of Cancer,* 109(11), pp. 2904-2910. doi: 10.1038/bjc.2013.667.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A. and Jemal, A. (2018) 'Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries', *CA: A Cancer Journal for Clinicians,* 68(6), pp. 394-424. doi: 10.3322/caac.21492.

Brener, N.D., Billy, J.O.G. and Grady, W.R. (2003) Assessment of factors affecting the validity of self-reported health-risk behavior among adolescents: evidence from the scientific literature, *Journal of Adolescent Health,* 33(6), pp. 436-457. doi: 10.1016/S1054-139X(03)00052-1

Broadbent, A. (2009) 'Causation and models of disease in epidemiology', *Studies in History and Philosophy of Biol & Biomed Sci,* 40(4), pp. 302-311. doi: 10.1016/j.shpsc.2009.09.006.

Brook, J.S., Duan, T., Brook, D.W. and Ning, Y. (2007) 'Pathways to nicotine dependence in African American and Puerto Rican young adults', *The American Journal on Addictions,* 16(6), pp. 450-456. doi: 10.1080/10550490701641132.

Brown, L.M., Gridley, G., Diehl, S.R., Winn, D.M., Harty, L.C., Otero, E.B., Fraumeni, J.F. and Hayes, R.B. (2001) 'Family cancer history and susceptibility to oral carcinoma in Puerto Rico', *Cancer,* 92(8), pp. 2102-2108.

Bruce, N., Pope, D. and Stanistreet, D. (2018) Quantitative Methods for Health Research. Newark: John Wiley & Sons, Incorporated.

Bush, J., White, M., Kai, J., Rankin, J. and Bhopal, R. (2003) 'Understanding influences on smoking in Bangladeshi and Pakistani adults: community based, qualitative study', *BMJ,* 326(7396), pp. 962-965. doi: 10.1136/bmj.326.7396.962.

Byakodi, R., Byakodi, S., Hiremath, S., Byakodi, J., Adaki, S., Marathe, K. and Mahind, P. (2012) 'Oral Cancer in India: An Epidemiologic and Clinical Review', *Journal of community health,* 37(2), pp. 319 4p. doi: 10.1007/s10900-011-9447-6.

Campaign for tobacco-free kids (2017) *Tobacco control legislation by country: Country details for Bangladesh* Available at: https://www.tobaccocontrollaws.org/legislation/country/bangladesh/summary (Accessed: July 19, 2018).

Carlson, M.D.A. and Morrison, R.S. (2009) 'Study design, precision, and validity in observational studies', *Journal of palliative medicine,* 12(1), pp. 77-82. doi: 10.1089/jpm.2008.9690.

Centre for Disease Control and Prevention (2012) *Social, Environmental, Cognitive, and Genetic Influences on the Use of Tobacco Among Youth.* US: Centers for Disease Control and Prevention (US). Available at: https://www.ncbi.nlm.nih.gov/books/NBK99236/ (Accessed: July 15, 2018).

Centre for Disease Control and Prevention (2018a)., 'Smokeless Tobacco: Products and Marketing' [Online] Available at: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/smokeless/products_marketing/index.htm (Accessed: June 19, 2019).

Centre for Disease Control and Prevention (2018b) About Adult BMI | Healthy Weight | CDC. Available at: https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html (Accessed: May 21, 2020).

Chaffee, B.W., Couch, E.T., Urata, J., Gansky, S.A., Essex, G. and Cheng, J. (2019) 'Predictors of Smokeless Tobacco Susceptibility, Initiation, and Progression Over Time Among Adolescents in a Rural Cohort', *Substance Use & Misuse,* 54(7), pp. 1154-1166. doi: 10.1080/10826084.2018.1564330.

Chaitanya, N., Boringi, M., Madathanapalle, R., Renee, A., Sree, S., Priyanka, N., Sownetha, T. and Marella, K. (2018) 'The Prevalence of Dental Caries in Smokers and Smokeless Tobacco Users', *Dental Hypotheses*, 9(2), pp. 36.

Chang, J.S., Lo, H., Wong, T., Huang, C., Lee, W., Tsai, S., Chen, K., Yen, C., Wu, Y., Hsueh, W., Yang, M., Wu, S., Chang, K., Chang, J., Ou, C., Wang, Y., Weng, Y., Yang, H., Wang, F., Lin, C., Huang, J. and Hsiao, J. (2013) 'Investigating the association between oral hygiene and head and neck cancer', *Oral Oncology,* 49(10), pp. 1010-1017. doi: 10.1016/j.oraloncology.2013.07.004.

Chatterjee, N., Todankar, P., Mandal, G., Gupte, H., Thawal, V., Bhutia, T. and Choudhuri, L. (2016) 'Factors Associated with Tobacco Use in Students Attending Local Government Schools in Mumbai, India', *Asian Pacific journal of cancer prevention : APJCP,* 17(12), pp. 5075.

Chaturvedi, P., Sarin, A., Seth, S.S. and Gupta, P.C. (2017) India: steep decline in tobacco consumption in India reported in second Global Adult Tobacco Survey (GATS 2017). Available at: http://nrs.harvard.edu/urn-3:HUL.InstRepos:34853158 (Accessed: 15/11/2020)

Chaturvedi, P., Sarin, A., Seth, S.S. and Gupta, P.C. (2017) India: steep decline in tobacco consumption in India reported in second Global Adult Tobacco Survey

(GATS 2017). Available at: http://nrs.harvard.edu/urn-3:HUL.InstRepos:34853158 (Accessed: .

Chen, F., He, B.-., Yan, L.-., Qiu, Y., Lin, L.-. and Cai, L. (2017a) 'Influence of oral hygiene and its interaction with standard of education on the risk of oral cancer in women who neither smoked nor drank alcohol: a hospital-based, case-control study', *The British Journal of Oral & Maxillofacial Surgery,* 55(3), pp. 260-265. doi: 10.1016/j.bjoms.2016.11.316.

Chen, F., Yan, L., Lin, L., Liu, F., Qiu, Y., Wang, J., Wu, J., Liu, F., Huang, J., Cai, L. and He, B. (2017b) 'Dietary score and the risk of oral cancer: a case-control study in southeast China', *Oncotarget,* 8(21), pp. 34610-34616. doi: 10.18632/oncotarget.16659.

Chen, P., Chiou, H. and Chen, Y. (2008) 'Chinese version of the Global Youth Tobacco Survey: cross-cultural instrument adaptation', *BMC public health,* 8(1), pp. 144. doi: 10.1186/1471-2458-8-144.

Chen, P., Mahmood, Q., Mariottini, G.L., Chiang, T. and Lee, K. (2017) *Adverse Health Effects of Betel Quid and the Risk of Oral and Pharyngeal Cancers.* Available at: https://www.hindawi.com/journals/bmri/2017/3904098/ (Accessed: Oct 26, 2019).

Cheong, S.C., Vatanasapt, P., Yi-Hsin, Y., Zain, R.B., Kerr, A.R. and Johnson, N.W. (2017) 'Oral cancer in South East Asia', *Translational Research in Oral Oncology,* 2, pp. 2057178. doi: 10.1177/2057178X17702921.

Choi, H.J., Yu, M. and Sacco, P. (2018) 'Racial and ethnic differences in patterns of adolescent tobacco users: A latent class analysis', *Children and Youth Services Review,* 84, pp. 86-93. doi: 10.1016/j.childyouth.2017.11.019.

Choudhury, K., Hanifi, S.M.A., Mahmood, S.S. and Bhuiya, A. (2007) 'Sociodemographic characteristics of tobacco consumers in a rural area of Bangladesh', *Journal of health, population, and nutrition,* 25(4), pp. 456-464.

Chowdhury, T.A. (2016) 'Adolescent Health in Bangladesh', *Journal of Bangladesh College of Physicians and Surgeons,* 33(1), pp. 1. doi: 10.3329/jbcps.v33i1.27953.

Christen, A.G., Swanson, B.Z., Glover, E.D. and Henderson, A.H. (1982) 'Smokeless Tobacco: The Folklore and Social History of Snuffing, Sneezing, Dipping, and Chewing', *The Journal of the American Dental Association,* 105(5), pp. 821-829. doi: 10.14219/jada.archive.1982.0453.

Colilla, S.A. (2010) 'An epidemiologic review of smokeless tobacco health effects and harm reduction potential', *Regulatory Toxicology and Pharmacology*, 56(2), pp. 197-211. doi: 10.1016/j.yrtph.2009.09.017.

Collins, J.A. and Fauser, B.C.J.M. (2005) 'Balancing the strengths of systematic and narrative reviews', Human reproduction update, 11(2), pp. 103-104. doi: 10.1093/humupd/dmh058.

Colvin, P.J. and Mermelstein, R.J. (2010) 'Adolescents' smoking outcome expectancies and acute emotional responses following smoking', *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 12(12), pp. 1203-1210. doi: 10.1093/ntr/ntq169.

Connelly, L.M. (2011) 'Cronbach's alpha', *Medsurg nursing : official journal of the Academy of Medical-Surgical Nurses,* 20(1), pp. 44.

Conrad, K.M., Flay, B.R. and Hill, D. (1992) 'Why children start smoking cigarettes: predictors of onset', *British journal of addiction,* 87(12), pp. 1711-1724. doi: 10.1111/j.1360-0443.1992.tb02684.x.

Creamer, M.R., Delk, J., Case, K., Perry, C.L. and Harrell, M.B. (2017) 'Positive Outcome Expectations and Tobacco Product Use Behaviors in Youth', *Substance Use & Misuse,* 53(8), pp. 1399-1402. doi: 10.1080/10826084.2017.1404104.

Creath, C.J., Cutter, G., Bradley, D.H. and Wright, J.T. (1991) 'Oral leukoplakia and adolescent smokeless tobacco use', *Oral Surgery, Oral Medicine, and Oral Pathology,* 72(1), pp. 35-41.

Czerninski, R., Zini, A. and Sgan-Cohen, H.D. (2010) 'Lip cancer: incidence, trends, histology and survival: 19702006', *British Journal of Dermatology,* 162(5), pp. 1103-1109. doi: 10.1111/j.1365-2133.2010.09698.x.

Daniel, W.W. (2009) *Biostatistics.* 9. ed. edn. Hoboken, NJ: Wiley.

Dasgupta, A., Karmakar, A., Bandyopadhyay, L., Garg, S., Paul, B. and Dey, A. (2017) 'How vulnerable are our adolescents to noncommunicable diseases? A school-based study in Kolkata', *International Journal of Health & Allied Sciences,* 6(4), pp. 199. doi: 10.4103/ijhas.IJHAS_52_17.

Desai, R., Mercken, L.A.G., Ruiter, R.A.C., Schepers, J. and Reddy, P.S. (2019) 'Cigarette smoking and reasons for leaving school among school dropouts in South Africa', BMC public health, 19(1), pp. 130. doi: 10.1186/s12889-019-6454-5.

Desai, R., Mercken, L.A.G., Ruiter, R.A.C., Schepers, J. and Reddy, P.S. (2019) 'Cigarette smoking and reasons for leaving school among school dropouts in South Africa', BMC public health, 19(1), pp. 130. doi: 10.1186/s12889-019-6454-5.

Devkota, S. and Panda, B. (2016) 'Socioeconomic gradients in early childhood health: evidence from Bangladesh and Nepal', *International Journal for Equity in Health,* 15, pp. 78. doi: 10.1186/s12939-016-0364-2.

Dholam, K.P. and Chouksey, G.C. (2016) 'Squamous cell carcinoma of the oral cavity and oropharynx in patients aged 18-45 years: A case-control study to evaluate the risk factors with emphasis on stress, diet, oral hygiene, and family history', *Indian Journal of Cancer,* 53(2), pp. 244-251. doi: 10.4103/0019-509X.197725.

Dikshit, R.P. and Kanhere, S. (2000) 'Tobacco habits and risk of lung, oropharyngeal and oral cavity cancer: a population-based case-control study in Bhopal, India', *International journal of epidemiology,* 29(4), pp. 609-614. doi: 10.1093/ije/29.4.609.

Diz, P., Meleti, M., Diniz-Freitas, M., Vescovi, P., Warnakulasuriya, S., Johnson, N.W. and Kerr, A.R. (2017) 'Oral and pharyngeal cancer in Europe', *Translational Research in Oral Oncology,* 2, pp. 2057178. doi: 10.1177/2057178X17701517.

Doku, D., Koivusilta, L., Raisamo, S. and Rimpelä, A. (2010) 'Do socioeconomic differences in tobacco use exist also in developing countries? A study of Ghanaian adolescents', *BMC public health,* 10(1), pp. 758. doi: 10.1186/1471-2458-10-758.

Du, X., Squier, C.A., Kremer, M.J. and Wertz, P.W. (2000) 'Penetration of N-nitrosonornicotine (NNN) across oral mucosa in the presence of ethanol and nicotine', *Journal of Oral Pathology & Medicine: Official Publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology,* 29(2), pp. 80-85.

Ebbert, J.O., Elrashidi, M.Y. and Stead, L.F. (2015) 'Interventions for smokeless tobacco use cessation', *The Cochrane database of systematic reviews,* (10), pp. CD004306. doi: 10.1002/14651858.CD004306.pub5.

Ebbert, Jon O. Severson, Herbert H. Danaher, Brian G. Schroeder, Darrell R. Glover, Elbert D (2012) 'A comparison of three smokeless tobacco dependence measures', *Addictive Behaviors,* 37(11), pp. 1271-1277. doi: 10.1016/j.addbeh.2012.06.011.

Ebrahim, S., Pearce, N., Smeeth, L., Casas, J.P., Jaffar, S. and Piot, P. (2013) 'Tackling Non-Communicable Diseases In Low- and Middle-Income Countries: Is the Evidence from High-Income Countries All We Need?', *PLOS Medicine,* 10(1), pp. e1001377. doi: 10.1371/journal.pmed.1001377.

Edefonti, V., Bravi, F., Vecchia, C.L., Randi, G., Ferraroni, M., Garavello, W., Franceschi, S., Talamini, R., Boffetta, P. and Decarli, A. (2010) 'Nutrient-based dietary patterns and the risk of oral and pharyngeal cancer', *Oral Oncology,* 46(5), pp. 343-348. doi: 10.1016/j.oraloncology.2009.11.017.

Edmundson, W.F. (1948) 'Microscopic grading of cancer and its practical implication', *Archives of Dermatology and Syphilology,* 57(2), pp. 141-150. doi: 10.1001/archderm.1948.01520140003001.

Efroymson, D., Buddhadeb, B. and Ruma, S. (2007) *The Economic Contribution of Women in Bangladesh Through their Unpaid Labor.* Dhaka: Helathbridge. Available at: https://healthbridge.ca/images/uploads/library/economic_contribution_report.pdf (Accessed: Apr 05, 2020).

El-Amin, S.E., Nwaru, B.I., Ginawi, I., Pisani, P. and Hakama, M. (2011) 'The role of parents, friends and teachers in adolescents' cigarette smoking and tombak dipping in Sudan', *Tobacco Control,* 20(2), pp. 94-99. doi: 10.1136/tc.2010.038091.

Ernani, V. and Saba, N.F. (2015) 'Oral Cavity Cancer: Risk Factors, Pathology, and Management', *Oncology,* 89(4), pp. 187-195. doi: 10.1159/000398801.

Etu, E.S., Gemeda, D.H. and Hussen, M.A. (2017) 'Prevalence and factors that influence smokeless tobacco use among adults in pastoralist communities of Borena Zone, Ethiopia: mixed method study', *Tobacco Induced Diseases,* 15(1). doi: 10.1186/s12971-016-0106-7.

Faruque, G.M., Wadood, S.N., Ahmed, M., Parven, R., Huq, I. and Chowdhury, S.R. (2019) *The cost of tobacco use is rising in Bangladesh.* Dhaka, Bangladesh: Cancer Research UK.
Availableat: https://www.cancerresearchuk.org/sites/default/files/tat004_factsheet_proactt_final_print.pdf (Accessed: March 18, 2010)

Filomeno, M., Bosetti, C., Garavello, W., Levi, F., Galeone, C., Negri, E. and La Vecchia, C. (2014) 'The role of a Mediterranean diet on the risk of oral and pharyngeal cancer', *British Journal of Cancer*, 111(5), pp. 981-986. doi: 10.1038/bjc.2014.329.

Finfgeld, D.L., Wongvatunyu, S., Conn, V.S., Grando, V.T. and Russell, C.L. (2003) 'Health Belief Model and Reversal Theory: a comparative analysis', *Journal of Advanced Nursing*, 43(3), pp. 288-297. doi: 10.1046/j.1365-2648.2003.02712.x.

Fisher, M.A., Taylor, G.W. and Tilashalski, K.R. (2005) 'Smokeless tobacco and severe active periodontal disease, NHANES III', *Journal of dental research,* 84(8), pp. 705.

Fitzmaurice, C., Allen, C., Barber, R.M., *et al.,* (2017) 'Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study', *JAMA oncology,* 3(4), pp. 524-548. doi: 10.1001/jamaoncol.2016.5688.

Flay, B., Petraitis, J. and Hu, F. (1999) 'Psychosocial risk and protective factors for adolescent tobacco use', *Nicotine & Tobacco Research,* 1(Supplement 1), pp. S59-S65. doi: 10.1080/14622299050011611.

Fleiss, J.L., Levin, B.A. and Paik, M.C. (2003) *Statistical methods for rates and proportions.* 3. ed. edn. Hoboken, NJ: Wiley.

Flora, M.S., Mascie-Taylor, C.G.N. and Rahman, M. (2009) 'Gender and locality differences in tobacco prevalence among adult Bangladeshis', *Tobacco Control,* 18(6), pp. 445-450. doi: 10.1136/tc.2008.028142.

Franceschi, S., Barra, S., La Vecchia, C., Bidoli, E., Negri, E. and Talamini, R. (1992) 'Risk factors for cancer of the tongue and the mouth. A case-control study from northern Italy', *Cancer,* 70(9), pp. 2227-2233. doi: AID-CNCR2820700902>3.0.CO;2-Z.

Franceschi, S., Levi, F., Dal Maso, L., Talamini, R., Conti, E., Negri, E. and La Vecchia, C. (2000) 'Cessation of alcohol drinking and risk of cancer of the oral cavity and pharynx', *International Journal of Cancer,* 85(6), pp. 787-790. doi: AID-IJC8>3.0.CO;2-6.

Fu, J.Y., Gao, J., Zhang, Z.Y., Zheng, J.W., Zhong, L.P., Luo, J.F. and Xiang, Y.B. (2013) 'Role of cigarette filter on the risk of oral cancer: a case-control study in a Chinese population', *Oral Diseases,* 19(1), pp. 80-84. doi: 10.1111/j.1601-0825.2012.01959.x.

Furberg, H., Lichtenstein, P., Pedersen, N.L., Bulik, C. and Sullivan, P.F. (2006) 'Cigarettes and oral snuff use in Sweden: prevalence and transitions', *Addiction,* 101(10), pp. 1509-1515.

Furman, K. (2017) 'Mono-Causal and Multi-Causal Theories of Disease: How to Think Virally and Socially about the Aetiology of AIDS', *Journal of Medical Humanities,* 56(2). doi: //doi.org/10.1007/s10912-017-9441-9.

Gamage, A.U. and Jayawardana, P.L. (2017) 'Knowledge of non-communicable diseases and practices related to healthy lifestyles among adolescents, in state schools of a selected educational division in Sri Lanka', *BMC public health,* 18(1), pp. 64-9. doi: 10.1186/s12889-017-4622-z.

Garavello, W., Foschi, R., Talamini, R., Vecchia, C.L., Rossi, M., Maso, L.D., Tavani, A., Levi, F., Barzan, L., Ramazzotti, V., Franceschi, S. and Negri, E. (2008) 'Family history and the risk of oral and pharyngeal cancer', *International Journal of Cancer,* 122(8), pp. 1827-1831. doi: 10.1002/ijc.23199.

Garrote, L.F., Herrero, R., Reyes, R.M., Vaccarella, S., Anta, J.L., Ferbeye, L., Muñoz, N. and Franceschi, S. (2001) 'Risk factors for cancer of the oral cavity and oro-pharynx in Cuba', *British Journal of Cancer*, 85(1), pp. 46-54. doi: 10.1054/bjoc.2000.1825.

Gaudet, M.M., Olshan, A.F., Chuang, S., *et al*. (2010) 'Body mass index and risk of head and neck cancer in a pooled analysis of case-control studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium', *International Journal of Epidemiology,* 39(4), pp. 1091-1102. doi: 10.1093/ije/dyp380.

Gendall, P., Hoek, J., Marsh, L., Edwards, R. and Healey, B. (2014) 'Youth tobacco access: trends and policy implications', *BMJ Open,* 4(4), pp. e004631. doi: 10.1136/bmjopen-2013-004631.

Genilo, J.W.R. and Sharif, M.R. (2016) 'Tobacco industry governance and responsibility discourses in Bangladesh', *South East Asia Journal of Public Health,* 5(2), pp. 13. doi: 10.3329/seajph.v5i2.28308.

Gerstman, B.B. (2013) Epidemiology Kept Simple. 3. Aufl. edn. Hoboken: Wiley-Blackwell.

Ghajari, H., Yousefi, F., Taymoori, P., Mohammadi, S., Nouri, B., Valizade, R. and Ghaderi, N. (2017) 'Predictors of smoking among the secondary high school boy students based on the health belief model.(Original Article)', *International Journal of Preventive Medicine,* 8(1), pp. 24. doi: 10.4103/ijpvm.IJPVM_264_16.

Ghantous, Y., Yaffi, V. and Abu-Elnaaj, I. (2015) 'Oral cavity cancer: epidemiology and early diagnosis', *Refu'at ha-peh veha-shinayim* (1993), 32(3), pp. 55.

Giovino, G.A., Mirza, S.A., Samet, J.M., Gupta, P.C., Jarvis, M.J., Bhala, N., Peto, R., Zatonski, W., Hsia, J., Morton, J., Palipudi, K.M. and Asma, S. (2012) 'Tobacco use in 3 billion individuals from 16 countries: an analysis of nationally representative cross-sectional household surveys', *Lancet (London, England),* 380(9842), pp. 668-679. doi: 10.1016/S0140-6736(12)61085-X.

Glanz, K., Rimer, B.K. and Viswanath, K. (2015) *Health Behaviour.* Fifth edit edn. New York, NY: Jossey Bass Ltd.

Global Youth Tobacco Survey Collaborative Group. (2012) 'Global Youth Tobacco Survey (GYTS): core questionnaire with optional questions. Version 1.0'. Available at https:// www.datafirst.uct.ac.za/ dataportal/ index.php/ catalog/ 645/ download/ 9102. (Accessed: May 13, 2015)

Goebel, L.J., Crespo, R.D., Abraham, R.T., Masho, S.W. and Glover, E.D. (2000) 'Correlates of youth smokeless tobacco use', *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 2(4), pp. 319-325. doi: 10.1080/713688153.

Goel, S., Kumar, R., Lal, P. and Singh, R. (2016) 'How effective is tobacco control enforcement to protect minors: Results from subnational surveys across four districts in India', *International Journal of Noncommunicable Diseases,* 1(3), pp. 116. doi: 10.4103/2468-8827.198583.

Going, R.E., Hsu, S.C., Pollack, R.L. and Haugh, L.D. (1980) 'Sugar and Fluoride Content of Various Forms of Tobacco', *The Journal of the American Dental Association*, 100(1), pp. 27-33. doi: 10.14219/jada.archive.1980.0028.

Goldstein, A.M., Blot, W.J., Greenberg, R.S., Schoenberg, J.B., Austin, D.F., Preston-Martin, S., Winn, D.M., Bernstein, L., McLaughlin, J.K. and Fraumeni, J.F. (1994) 'Familial risk in oral and pharyngeal cancer', *European Journal of Cancer. Part B, Oral Oncology,* 30B(5), pp. 319-322.

Gourab, D. and Chowdhury, F.R. (2015) 'Alcohol Use and Alcohol Use Disorders in Bangladesh', *Asia Pacific Journal of Medical Toxicology,* 4(2), pp. 83-90. doi: 10.22038/apjmt.2015.5091.

Goyal, G. (2016) 'Knowledge, Attitude and Practice of Chewing Gutka, Areca Nut, Snuff and Tobacco Smoking Among the Young Population in the Northern India Population', *Asian Pacific journal of cancer prevention : APJCP,* 17(11), pp. 4813-4818. doi: 10.22034/APJCP.2016.17.11.4813.

Green, B.N., Johnson, C.D. and Adams, A. (2006) 'Writing narrative literature reviews for peer-reviewed journals: secrets of the trade', Journal of chiropractic medicine, 5(3), pp. 101-117. doi: 10.1016/s0899-3467(07)60142-6.

Greene, J.C., Ernster, V.L., Grady, D.G., Robertson, P.B., Walsh, M.M. and Stillman, L.A. (2011) *Clinical and Pathological Effects CONTENTS Oral Mucosal Lesions:*

Clinical Findings in Relation to Smokeless Tobacco Use Among U.S. Baseball Players.

Greer, R.O. (2011) 'Oral Manifestations of Smokeless Tobacco Use', *Otolaryngologic Clinics of North America,* 44(1), pp. 31-56. doi: 10.1016/j.otc.2010.09.002.

Griesler, P.C., Hu, M. and Kandel, D.B. (2016) 'Nicotine Dependence in Adolescence and Physical Health Symptoms in Early Adulthood', *Nicotine & Tobacco Research,* 18(5), pp. 950-958. doi: 10.1093/ntr/ntv149.

Grimes, D.A. and Schulz, K.F. (2002) 'Bias and causal associations in observational research', *The Lancet,* 359(9302), pp. 248-252. doi: 10.1016/S0140-6736(02)07451-2.

Grimes, D.A. and Schulz, K.F. (2005) 'Compared to what? Finding controls for case-control studies', *The Lancet,* 365(9468), pp. 1429-1433. doi: 10.1016/S0140-6736(05)66379-9.

Guha, N., Warnakulasuriya, S., Vlaanderen, J. and Straif, K. (2014) 'Betel quid chewing and the risk of oral and oropharyngeal cancers: A meta-analysis with implications for cancer control', *International Journal of Cancer,* 135(6), pp. 1433-1443. doi: 10.1002/ijc.28643.

Guily, J.L.S., Jacquard, A., Prétet, J., Haesebaert, J., Beby-Defaux, A., Clavel, C., Agius, G., Birembaut, P., Okaïs, C., Léocmach, Y., Soubeyrand, B., Pradat, P., Riethmuller, D., Mougin, C. and Denis, F. (2011) 'Human papillomavirus genotype distribution in oropharynx and oral cavity cancer in France--The EDiTH VI study', *Journal of Clinical Virology: The Official Publication of the Pan American Society for Clinical Virology,* 51(2), pp. 100-104. doi: 10.1016/j.jcv.2011.03.003.

Gupta, B. and Johnson, N.W. (2014) 'Systematic Review and Meta-Analysis of Association of Smokeless Tobacco and of Betel Quid without Tobacco with Incidence of Oral Cancer in South Asia and the Pacific', *PloS one,* 9(11), pp. e113385. doi: 10.1371/journal.pone.0113385.

Gupta, B., Bray, F., Kumar, N. and Johnson, N.W. (2017) 'Associations between oral hygiene habits, diet, tobacco and alcohol and risk of oral cancer: A case-control study from India', *Cancer Epidemiology,* 51, pp. 7-14. doi: 10.1016/j.canep.2017.09.003.

Gupta, B., Kumar, N. and Johnson, N. (2017) 'Relationship of lifetime exposure to tobacco, alcohol and second-hand tobacco smoke with upper aero-digestive tract cancers in India: A case-control study with a life-course perspective', *Asian Pacific Journal of Cancer Prevention,* 18(2), pp. 347-356. doi: 10.22034/APJCP.2017.18.2.347.

Gupta, N., Gupta, R., Acharya, A.K., Patthi, B., Goud, V., Reddy, S., Garg, A. and Singla, A. (2016) 'Changing Trends in Oral Cancer - A Global Scenario' *Nepal journal of epidemiology*, 6(4), pp. 613-619.

Gupta, P.C. and RAY, C.S. (2003) 'Smokeless tobacco and health in India and South Asia', *Respirology,* 8(4), pp. 419-431. doi: 10.1046/j.1440-1843.2003.00507.x.

Gupta, P.C. and Ray, C.S. (2004) 'Epidemiology of betel quid usage', *Annals of the Academy of Medicine,* Singapore, 33(4 Suppl), pp. 31.

Gupta, S., Gupta, R., Sinha, D.N. and Mehrotra, R. (2018) 'Relationship between type of smokeless tobacco & risk of cancer: A systematic review', *The Indian Journal of Medical Research*, 148(1), pp. 56-76. doi: 10.4103/ijmr.IJMR_2023_17.

Gupta, V., Kumar, P., s. Yadav, Khattar, A. and Tyagi, S. (2012) 'Oral cancer as a leading annoyance of the South Asian territory: An epidemiologic and clinical review', *Clinical Cancer Investigation Journal,* 1(4), pp. 196-200.

Hahn, G., Charlin, V.L., Sussman, S., Dent, C.W., Manzi, J., Stacy, A.W., Flay, B., Hansen, W.B. and Burton, D. (1990) 'Adolescents' first and most recent use situations of smokeless tobacco and cigarettes: Similarities and differences', *Addictive Behaviors,* 15(5), pp. 439-448. doi: 10.1016/0306-4603(90)90030-2.

Haque, N., Uddin, A.F.M.K., Dey, B.R., Islam, F. and Goodman, A. (2017) 'Challenges to cervical cancer treatment in Bangladesh: The development of a women's cancer ward at Dhaka Medical College Hospital', *Gynecologic Oncology Reports,* 21(C), pp. 67-72. doi: 10.1016/j.gore.2017.06.001.

Harrabi, I., Maatoug, J., Gaha, M., Kebaili, R., Gaha, R. and Ghannem, H. (2010) 'School-based Intervention to Promote Healthy Lifestyles in Sousse, Tunisia', *Indian Journal of Community Medicine: Official Publication of Indian Association of Preventive & Social Medicine,* 35(1), pp. 94-99. doi: 10.4103/0970-0218.62581.

Hashibe, M., Brennan, P., Benhamou, S., Castellsague, X., Chen, C., Curado, M.P., Maso, L.D., Daudt, A.W., Fabianova, E., Wünsch-Filho, V., Franceschi, S., Hayes, R.B., Herrero, R., Koifman, S., Vecchia, C.L., Lazarus, P., Levi, F., Mates, D., Matos, E., Menezes, A., Muscat, J., Eluf-Neto, J., Olshan, A.F., Rudnai, P., Schwartz, S.M., Smith, E., Sturgis, E.M., Szeszenia-Dabrowska, N., Talamini, R., Wei, Q., Winn, D.M., Zaridze, D., Zatonski, W., Zhang, Z., Berthiller, J. and Boffetta, P. (2007) 'Alcohol Drinking in Never Users of Tobacco, Cigarette Smoking in Never Drinkers, and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium', *Journal of the National Cancer Institute,* 99(10), pp. 777-789. doi: 10.1093/jnci/djk179.

Hashibe, M., Brennan, P., Chuang, S., Boccia, S., Castellsague, X., Chen, C., Curado, M.P., Maso, L.D., Daudt, A.W., Fabianova, E., Fernandez, L., Wünsch-Filho, V., Franceschi, S., Hayes, R.B., Herrero, R., Kelsey, K., Koifman, S., Vecchia, C.L., Lazarus, P., Levi, F., Lence, J.J., Mates, D., Matos, E., Menezes, A., McClean, M.D., Muscat, J., Eluf-Neto, J., Olshan, A.F., Purdue, M., Rudnai, P., Schwartz, S.M., Smith, E., Sturgis, E.M., Szeszenia-Dabrowska, N., Talamini, R., Wei, Q., Winn, D.M., Shangina, O., Pilarska, A., Zhang, Z., Ferro, G., Berthiller, J. and Boffetta, P. (2009) 'Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium', *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the*

American Society of Preventive Oncology, 18(2), pp. 541-550. doi: 10.1158/1055-9965.EPI-08-0347.

Hashim, D., Sartori, S., Brennan, P., Curado, M.P., Wünsch-Filho, V., Divaris, K., Olshan, A.F., Zevallos, J.P., Winn, D.M., Franceschi, S., Castellsagué, X., Lissowska, J., Rudnai, P., Matsuo, K., Morgenstern, H., Chen, C., Vaughan, T.L., Hofmann, J.N., D'Souza, G., Haddad, R.I., Wu, H., Lee, Y.-., Hashibe, M., Vecchia, C.L. and Boffetta, P. (2016) 'The role of oral hygiene in head and neck cancer: results from International Head and Neck Cancer Epidemiology (INHANCE) consortium', *Annals of Oncology: Official Journal of the European Society for Medical Oncology,* 27(8), pp. 1619-1625. doi: 10.1093/annonc/mdw224.

Hassan, E. (2005) 'Recall Bias can be a Threat to Retrospective and Prospective Research Designs ', *The Internet Journal of Epidemilogy,* 3(2).

Hatsukami, D.K., Ebbert, J.O., Feuer, R.M., Stepanov, I. and Hecht, S.S. (2007) 'Changing smokeless tobacco products new tobacco-delivery systems', *American Journal of Preventive Medicine,* 33(6 Suppl), pp. 368. doi: 10.1016/j.amepre.2007.09.005.

Hawkins, R.J., Wang, E.E. and Leake, J.L. (1999) 'Preventive health care, 1999 update: prevention of oral cancer mortality. The Canadian Task Force on Preventive Health Care', *Journal (Canadian Dental Association),* 65(11), pp. 617.

Hawkins, S.S., Bach, N. and Baum, C.F. (2018) 'Impact of tobacco control policies on adolescent smokeless tobacco and cigar use: a difference-in-differences approach', *BMC Public Health,* 18(1), pp. 154. doi: 10.1186/s12889-018-5063-z.

Hebert, J.R., Gupta, P.C., Bhonsle, R.B., Mehta, H., Zheng, W., Sanderson, M. and Teas, J. (2002) 'Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India', *Public Health Nutrition,* 5(2), pp. 303-312. doi: 10.1079/PHN2002249.

Hecht, S.S. (1999) 'Tobacco smoke carcinogens and lung cancer', Journal of the National Cancer Institute, 91(14), pp. 1194-1210. doi: 10.1093/jnci/91.14.1194.

Heck, J.E., Marcotte, E.L., Argos, M., Parvez, F., Ahmed, A., Islam, T., Sarwar, G., Hasan, R., Ahsan, H. and Chen, Y. (2012) 'Betel quid chewing in rural Bangladesh: prevalence, predictors and relationship to blood pressure', *International journal of epidemiology,* 41(2), pp. 462-471. doi: 10.1093/ije/dyr191.

Hedman, L., Bjerg-Bäcklund, A., Perzanowski, M., Sundberg, S. and Rönmark, E. (2006) 'Factors related to tobacco use among teenagers', *Respiratory Medicine,* 101(3), pp. 496-502. doi: 10.1016/j.rmed.2006.07.001.

Hellqvist, L., Rolandsson, M., Hugoson, A., Lingström, P. and Birkhed, D. (2015) 'Dental caries and associated factors in a group of Swedish snus users', *Swedish dental journal,* 39(1), pp. 47-54.

Hennessy, S., Bilker, W.B., Berlin, J.A. and Strom, B.L. (1999) 'Factors influencing the optimal control-to-case ratio in matched case-control studies', *American* *journal of epidemiology,* 149(2), pp. 195-197. doi: 10.1093/oxfordjournals.aje.a009786.

Herrero, R., Castellsagué, X., Pawlita, M., Lissowska, J., Kee, F., Balaram, P., Rajkumar, T., Sridhar, H., Rose, B., Pintos, J., Fernández, L., Idris, A., Sánchez, M.J., Nieto, A., Talamini, R., Tavani, A., Bosch, F.X., Reidel, U., Snijders, P.J.F., Meijer, Chris J. L. M., Viscidi, R., Muñoz, N. and Franceschi, S. (2003) 'Human Papillomavirus and Oral Cancer: The International Agency for Research on Cancer Multicenter Study', JNCI: Journal of the National Cancer Institute, 95(23), pp. 1772-1783. doi: 10.1093/jnci/djg107.

Hiscock, R., Bauld, L., Amos, A., Fidler, J.A. and Munafò, M. (2012) 'Socioeconomic status and smoking: a review', *Annals of the New York Academy of Sciences,* 1248, pp. 107-123. doi: 10.1111/j.1749-6632.2011.06202.x.

Hoffmann, D. and Djordjevic, M.V. (1997) 'Chemical Composition and Carcinogenicity of Smokeless Tobacco', *Advances in Dental Research,* 11(3), pp. 322-329. doi: 10.1177/08959374970110030301.

Holmén, A., Strömberg, U., Magnusson, K. and Twetman, S. (2013) 'Tobacco use and caries risk among adolescents--a longitudinal study in Sweden', *BMC oral health,* 13(1), pp. 31. doi: 10.1186/1472-6831-13-31.

Horn, K.A., Gao, X., Dino, G.A. and Kamal-Bahl, S. (2000) 'Determinants of Youth Tobacco Use in West Virginia: A Comparison of Smoking and Smokeless Tobacco Use', *The American Journal of Drug and Alcohol Abuse,* 26(1), pp. 125-138. doi: 10.1081/ADA-100100595.

Hosmer, D.W., Lemeshow, S. and Sturdivant, R.X. (2013) *Applied logistic regression.* 3. ed. edn. Hoboken, NJ: Wiley.

Hossain, M.S., Kypri, K., Rahman, B., Akter, S. and Milton, A.H. (2016) 'Health knowledge and smokeless tobacco quit attempts and intentions among married women in rural Bangladesh: Cross-sectional survey', *Drug and Alcohol Review,* 35(5), pp. 514-522. doi: 10.1111/dar.12346.

Hossain, M.S., Kypri, K., Rahman, B., Arslan, I., Akter, S. and Milton, A.H. (2014) 'Prevalence and Correlates of Smokeless Tobacco Consumption among Married Women in Rural Bangladesh', *PLoS ONE,* 9(1), pp. 1-6. doi: 10.1371/journal.pone.0084470.

Hossain, M.T., Hassi, U. and Imamul Huq, S.M. (2018) 'Assessment of concentration and toxicological (Cancer) risk of lead, cadmium and chromium in tobacco products commonly available in Bangladesh', Toxicology reports, 5, pp. 897-902. doi: 10.1016/j.toxrep.2018.08.019.

Hu, F.B., Hedeker, D., Day, L.E., Flay, B.R., Siddiqui, O., Sussman, S. and Richardson, J. (1997) 'Patterns of use of smokeless tobacco and the unidimensional model of drug involvement', *Addictive Behaviors,* 22(2), pp. 257-261. doi: 10.1016/S0306-4603(96)00020-2.

Hugoson, A., Hellqvist, L., Rolandsson, M. and Birkhed, D. (2012) 'Dental caries in relation to smoking and the use of Swedish snus: epidemiological studies covering 20 years (1983-2003)', *Acta Odontologica Scandinavica,* 70(4), pp. 289-296. doi: 10.3109/00016357.2011.654247.

Huhtala, H.S.A., Rainio, S.U. and Rimpelä, A.H. (2006) 'Adolescent snus use in Finland in 1981-2003: trend, total sales ban and acquisition', *Tobacco Control,* 15(5), pp. 392-397. doi: 10.1136/tc.2005.015313.

Huque, R., Shah, S., Mushtaq, N. and Siddiqi, K. (2016) 'Determinants of Salivary Cotinine among Smokeless Tobacco Users: A Cross-Sectional Survey in Bangladesh', *PloS one,* 11(8), pp. e0160211. doi: 10.1371/journal.pone.0160211.

Huque, R., Zaman, M., Huq, S. and Sinha, D. (2017) 'Smokeless tobacco and public health in Bangladesh', *Indian Journal of Public Health,* 61(5), pp. 18-24. doi: 10.4103/ijph.IJPH_233_17.

Hussain, A., Zaheer, S. and Shafique, K. (2017) 'Individual, social and environmental determinants of smokeless tobacco and betel quid use amongst adolescents of Karachi: a school-based cross-sectional survey', *BMC public health,* 17(1), pp. 913. doi: 10.1186/s12889-017-4916-1.

IARC (1985) *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol.37 : tobacco habits other than smoking, betel-quid and areca-nut chewing, and some related nitrosamines.* Lyon: International Agency for Research on Cancer.

IARC (2004) 'Betel-quid and areca-nut chewing and some areca-nut derived nitrosamines', *IARC monographs on the evaluation of carcinogenic risks to humans,* 85, pp. 1-334.

IARC (2007) 'Smokeless tobacco and some tobacco-specific N-nitrosamines', *IARC monographs on the evaluation of carcinogenic risks to humans,* 89, pp. 1-592.

IARC (2008) *Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, Volume 89.* World Health Organisation.

IARC (2012) *IARC monographs on the evaluation of carcinogenic risks to humans, volume 100 E, personal habits and indoor combustions.* Lyon: IARC,.

IARC (2018) GLOBOCAN 2018: estimated cancer incidence, mortality and prevalence worldwide in 2018. Available at: https://gco.iarc.fr/ (Accessed: May 15, 2019).

Idris, A.M., Ahmed, H.M. and Malik, M.O. (1995) 'Toombak dipping and cancer of the oral cavity in the Sudan: a case-control study', *International journal of cancer,* 63(4), pp. 477-480. doi: 10.1002/ijc.2910630402.

Islam, J., Zaman, M., Bhuiyan, M., Ahsan, H., Rahman, M., Rahman, M.C. and M (2017) 'Alcohol consumption among adults in Bangladesh: results from STEPS 2010 ', *South-Asia Journal of Public Health,* 6(1), pp. 67-74.

Islam, N. and Al-Khateeb, M. (1995) *Challenges and opportunities for tobacco control in the Islamic countries-a case-study from Bangladesh*. EMHJ - Eastern Mediterranean Health Journal, 1 (2), 230-234, 1995 https://apps.who.int/iris/handle/10665/118673

Islam, S.S., Mainuddin, A.K.M., Bhuiyan, F. and Chowdhury, K. (2016) 'Prevalence of tobacco use and its contributing factors among adolescents in Bangladesh: Results from a population-based study', *South Asian Journal of Cancer,* 5(4), pp. 186-188. doi: 10.4103/2278-330X.195339.

Itanyi, I.U., Onwasigwe, C.N., McIntosh, S., Bruno, T., Ossip, D., Nwobi, E.A., Onoka, C.A. and Ezeanolue, E.E. (2018) 'Disparities in tobacco use by adolescents in southeast, Nigeria using Global Youth Tobacco Survey (GYTS) approach', *BMC public health,* 18(1), pp. 317. doi: 10.1186/s12889-018-5231-1.

Janbaz, K.H., Qadir, M.I., Basser, H.T., Bokhari, T.H. and Ahmad, B. (2014) 'Risk for oral cancer from smokeless tobacco', *Contemporary Oncology / Wspolczesna Onkologia,* 18(3), pp. 160.

Javed, F., Correra, F.O.B., Chotai, M., Tappuni, A.R. and Almas, K. (2010) 'Systemic conditions associated with areca nut usage: a literature review', *Scandinavian Journal of Public Health,* 38(8), pp. 838-844. doi: 10.1177/1403494810379291.

Johnson, N. (2001) 'Tobacco use and oral cancer: a global perspective', *Journal of Dental Education,* 65(4), pp. 328-339.

Kabir, M.A., Goh, K. and Khan, M.M.H. (2015) 'Adolescent Tobacco Use and Its Determinants', *Asia-Pacific Journal of Public Health,* 27(2), pp. NP1590. doi: 10.1177/1010539512472357.

Kabir, M.I., Rahman, M.B., Smith, W., Lusha, M.A.F. and Milton, A.H. (2016) 'Climate change and health in Bangladesh: a baseline cross-sectional survey', Global Health Action, 9. doi: 10.3402/gha.v9.29609.

Kabwama, S.N., Ndyanabangi, S., Mutungi, G., Wesonga, R., Bahendeka, S.K. and Guwatudde, D. (2016) 'Tobacco use and associated factors among Adults in Uganda: Findings from a nationwide survey', *Tobacco induced diseases,* 14(1), pp. 27. doi: 10.1186/s12971-016-0093-8.

Kaduri, P., Kitu, H., Mbatia, J., Kitua, A.Y. and Mbwmbo, J. (2008) 'Smokeless tobacco use among adolescents in Ilala Municipality, Tanzania', *Tanzania Journal of Health Research,* 10(1), pp. 28.

Kaestle, C.E. (2009) 'How Girls and Boys Get Tobacco: Adults and Other Sources', *Journal of Adolescent Health*, 45(2), pp. 208-210. doi: 10.1016/j.jadohealth.2009.02.010.

Kakde, S., Bhopal, R.S. and Jones, C.M. (2012) 'A systematic review on the social context of smokeless tobacco use in the South Asian population: Implications for public health', *Public Health,* 126(8), pp. 635-645. doi: 10.1016/j.puhe.2012.05.002.

Kallischnigg, G., Weitkunat, R. and Lee, P.N. (2008) 'Systematic review of the relation between smokeless tobacco and non-neoplastic oral diseases in Europe and the United States', *BMC Oral Health,* 8, pp. 1.

Kaugars, G.E., Riley, W.T., Brandt, R.B., Burns, J.C. and Svirsky, J.A. (1992) 'The prevalence of oral lesions in smokeless tobacco users and an evaluation of risk factors', *Cancer,* 70(11), pp. 2579-2585.

Kawakita, D., Lee, Y.A., Li, Q., Chen, Y., Chen, C., Hsu, W., Lou, P., Zhu, C., Pan, J., Shen, H., Ma, H., Cai, L., He, B., Wang, Y., Zhou, X., Ji, Q., Zhou, B., Wu, W., Ma, J., Boffetta, P., Zhang, Z., Dai, M. and Hashibe, M. (2017) 'Impact of oral hygiene on head and neck cancer risk in a Chinese population', *Head & Neck,* 39(12), pp. 2549-2557. doi: 10.1002/hed.24929.

Kelder, S.H., Hoelscher, D., Perry, C.L. (2015). How individuals, environments, and health behaviors interact: Social cognitive theory. In Glanz, K., Rimer, B.K., Viswanath, K. (Ed.), Health behavior:

Keogh, R.H. and Cox, D.R. (2014) *Case-control studies.* Cambridge University Press.

Khan, A., Huque, R., Shah, S.K., Kaur, J., Baral, S., Gupta, P.C., Cherukupalli, R., Sheikh, A., Selvaraj, S., Nargis, N., Cameron, I. and Siddiqi, K. (2014) 'Smokeless Tobacco Control Policies in South Asia: A Gap Analysis and Recommendations', *Nicotine & Tobacco Research,* 16(6), pp. 890-894. doi: ge10.1093/ntr/ntu020.

Khan, Z. (2012) 'An Overview of Oral Cancer in Indian Subcontinent and Recommendations to Decrease its Incidence',.

Khan, Z. (2016) 'A gaping gap (smokeless tobacco control in Pakistan', *Tobacco Induced Diseases,* 14(1). doi: 10.1186/s12971-016-0102-y.

Khan, Z., Dreger, S., Shah, S.M.H., Pohlabeln, H., Khan, S., Ullah, Z., Rehman, B. and Zeeb, H. (2017) 'Oral cancer via the bargain bin: The risk of oral cancer associated with a smokeless tobacco product (Naswar)', *PLoS One,* 12(7), pp. e0180445. doi: 10.1371/journal.pone.0180445.

Khan, Z., Tönnies, J. and Müller, S. (2014) 'Smokeless tobacco and oral cancer in South Asia: a systematic review with meta-analysis', *Journal of Cancer Epidemiology,* 2014, pp. 394696. doi: 10.1155/2014/394696.

Ko, Y., Huang, Y., Lee, C., Chen, M., Lin, L. and Tsai, C. (1995) 'Betel quid chewing, cigarette smoking and alcohol consumption related to oral cancer in Taiwan', *Journal of Oral Pathology & Medicine,* 24(10), pp. 450-453. doi: 10.1111/j.1600-0714.1995.tb01132.x..

Kotwal A., Thakur R., Seth T (2005) 'Correlates of tobacco-use pattern amongst adolescents in two schools of New Delhi, India', *Indian Journal of Medical Sciences,* 59(6), pp. 243. doi: 10.4103/0019-5359.16299.

Kovács, E., Siani, A., Konstabel, K., Hadjigeorgiou, C., de Bourdeaudhuij, I., Eiben, G., Lissner, L., Gwozdz, W., Reisch, L., Pala, V., Moreno, L.A., Pigeot, I., Pohlabeln, H., Ahrens, W. and Molnár, D. (2014) 'Adherence to the obesity-related lifestyle intervention targets in the IDEFICS study', *International journal of obesity*, 38 Suppl 2(S2), pp. S144-S151. doi: 10.1038/ijo.2014.145.

Kreimer, A.R., Randi, G., Herrero, R., Castellsagué, X., Vecchia, C.L. and Franceschi, S. (2006) 'Diet and body mass, and oral and oropharyngeal squamous cell carcinomas: Analysis from the IARC multinational case–control study', *International Journal of Cancer,* 118(9), pp. 2293-2297. doi: 10.1002/ijc.21577.

Krieger, N. (1994) 'Epidemiology and the web of causation: Has anyone seen the spider?', *Social Science & Medicine,* 39(7), pp. 887-903. doi: 10.1016/0277-9536(94)90202-X.

Kujan, O., Farah, C.S. and Johnson, N.W. (2017) 'Oral and oropharyngeal cancer in the Middle East and North Africa', *Translational Research in Oral Oncology,* 2, pp. 2057178. doi: 10.1177/2057178X17698480.

Kumar, V., Talwar, R., Roy, N., Raut, D. and Singh, S. (2014) 'Psychosocial Determinants of Tobacco Use among School Going Adolescents in Delhi, India', *Journal of addiction,* 2014, pp. 170941.

Kuo, C., Duan, Y. and Grady, J. (2018) 'Unconditional or Conditional Logistic Regression Model for Age-Matched Case–Control Data?', *Frontiers in public health*, 6, pp. 57. doi: 10.3389/fpubh.2018.00057.

Kyle, R.G., Nicoll, A., Forbat, L. and Hubbard, G. (2013) 'Adolescents' awareness of cancer risk factors and associations with health-related behaviours', *Health education research,* 28(5), pp. 816-827. doi: 10.1093/her/cyt055.

LaMorte W. (2019) 'Behavioral Change Models-The Social Cognitive Theory' Available at: http://sphweb.bumc.bu.edu/otlt/MPH-Modules/SB/BehavioralChangeTheories/BehavioralChangeTheories5.html Accessed:July 17, 2019

Langlois, M.A., Petosa, R. and Hallam, J.S. (1999) 'Why Do Effective Smoking Prevention Programs Work? Student Changes in Social Cognitive Theory Constructs', *Journal of School Health,* 69(8), pp. 326-331. doi: 10.1111/j.1746-1561.1999.tb06423.x.

Laprise, C., Madathil, S.A., Allison, P., Abraham, P., Raghavendran, A., Shahul, H.P., ThekkePurakkal, A., Castonguay, G., Coutlée, F., Schlecht, N.F., Rousseau, M., Franco, E.L. and Nicolau, B. (2016) 'No role for human papillomavirus infection in oral cancers in a region in southern India', *International Journal of Cancer,* 138(4), pp. 912-917. doi: 10.1002/ijc.29827.

Laprise, C., Madathil, S.A., Schlecht, N.F., Castonguay, G., Soulières, D., Nguyen-Tan, P.F., Allison, P., Coutlée, F., Hier, M., Rousseau, M., Franco, E.L. and Nicolau, B. (2017) 'Human papillomavirus genotypes and risk of head and neck cancers: Results from the HeNCe Life case-control study', *Oral Oncology,* 69, pp. 56-61. doi: 10.1016/j.oraloncology.2017.03.013.

Larsman, P., Eklöf, M. and Törner, M. (2012) 'Adolescents' risk perceptions in relation to risk behavior with long-term health consequences; antecedents and outcomes: A literature review', *Safety Science,* 50(9), pp. 1740-1748. doi: 10.1016/j.ssci.2012.04.009.

Lashkari, K. and Shukla, A. (2016) 'Prevalence of Dental Caries among Smokeless Tobacco Chewers in Dakshina Kannada District Population: A Cross Sectional Study ', *OHDM,* 15(6), pp. 1-2.

Lauterstein, D., Hoshino, R., Gordon, T., Watkins, B., Weitzman, M. and Zelikoff, J. (2014) 'The changing face of tobacco use among United States youth', *Current drug abuse reviews,* 7(1), pp. 29.

Lawler, T.S., Stanfill, S.B., Zhang, L., Ashley, D.L. and Watson, C.H. (2013) 'Chemical characterization of domestic oral tobacco products: total nicotine, pH, unprotonated nicotine and tobacco-specific N-nitrosamines', *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association,* 57, pp. 380-386. doi: 10.1016/j.fct.2013.03.011.

Le Campion, Anna Carolina Omena Vasconcellos, Ribeiro, C.M.B., Luiz, R.R., da Silva Júnior, Francisco Feliciano, Barros, H.C.S., dos Santos, Karine de Cássia Batista, Ferreira, S.J., Gonçalves, L.S. and Ferreira, S.M.S. (2017) 'Low Survival Rates of Oral and Oropharyngeal Squamous Cell Carcinoma', *International Journal of Dentistry*, 2017, pp. 5815493-7. doi: 10.1155/2017/5815493.

Lee, C., Ko, A.M., Warnakulasuriya, K., Yin, B., Sunarjo, N.V., Zain, R.B., Ibrahim, S.O., Liu, Z., Li, W., Zhang, S., Kuntoro, N.V., Utomo, B., Rajapakse, P.S., Warusavithana, S.A., Razak, I.A., Abdullah, N., Shrestha, P., Kwan, A., Shieh, T., Chen, M. and Ko, Y. (2011) 'Intercountry prevalences and practices of betel-quid use in south, southeast and eastern asia regions and associated oral preneoplastic disorders: An international collaborative study by asian betel-quid consortium of south and east Asia' *International Journal of Cancer*, 129(7), pp. 1741-1751. doi: 10.1002/ijc.25809.

Lee, K. (2012) *The Philosophical Foundations of Modern Medicine.* London: Springer Nature.

Lee, P.N. and Hamling, J. (2009) 'Systematic review of the relation between smokeless tobacco and cancer in Europe and North America', *BMC Medicine,* 7, pp. 36. doi: 10.1186/1741-7015-7-36.

Lee, Y.A., Li, S., Chen, Y., Li, Q., Chen, C., Hsu, W., Lou, P., Zhu, C., Pan, J., Shen, H., Ma, H., Cai, L., He, B., Wang, Y., Zhou, X., Ji, Q., Zhou, B., Wu, W., Ma, J., Boffetta, P., Zhang, Z., Dai, M. and Hashibe, M. (2019) 'Tobacco smoking, alcohol drinking, betel quid chewing, and the risk of head and neck cancer in an East Asian population', *Head & Neck,* 41(1), pp. 92-102. doi: 10.1002/hed.25383.

Lee, Y.O., Hebert, C.J., Nonnemaker, J.M. and Kim, A.E. (2015) 'Youth Tobacco Product Use in the United States', *Pediatrics,* 135(3), pp. 409-415. doi: 10.1542/peds.2014-3202.

Leon, M.E., Lugo, A., Boffetta, P., Gilmore, A., Ross, H., Schüz, J., La Vecchia, C. and Gallus, S. (2016) 'Smokeless tobacco use in Sweden and other 17 European countries', *European Journal of Public Health,* 26(5), pp. 817-821. doi: 10.1093/eurpub/ckw032.

Levy, D.T., Mays, D., Boyle, R.G., Tam, J. and Chaloupka, F.J. (2017) 'The Effect of Tobacco Control Policies on US Smokeless Tobacco Use: A Structured Review', *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco,* 20(1), pp. 3-11. doi: 10.1093/ntr/ntw291.

Li, L., Zhang, M. and Holman, C.D.J. (2013) 'Hospital outpatients are satisfactory for case-control studies on cancer and diet in China: a comparison of population versus hospital controls', *Asian Pacific journal of cancer prevention : APJCP,* 14(5), pp. 2723-2729. doi: 10.7314/APJCP.2013.14.5.2723.

Lindenblatt, Rhayany de Castro Ribeiro, Martinez, G.L., Silva, L.E., Faria, P.S., Camisasca, D.R. and Lourenço, Simone de Queiroz Chaves (2012) 'Oral squamous cell carcinoma grading systems – analysis of the best survival predictor', *Journal of Oral Pathology & Medicine,* 41(1), pp. 34-39. doi: 10.1111/j.1600-0714.2011.01068.x..

Linetzky, B., Mejia, R., Ferrante, D., De Maio, F.G. and Diez Roux, A.V. (2012) 'Socioeconomic Status and Tobacco Consumption Among Adolescents: A Multilevel Analysis of Argentina's Global Youth Tobacco Survey', *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 14(9), pp. 1092-1099. doi: 10.1093/ntr/nts004.

Lipari, R.N. and Van, S.L.H. (2013) *Trends in Smokeless Tobacco Use and Initiation: 2002 to 2014.* Substance Abuse and Mental Health Services Administration (US), Rockville (MD).

Liu, S.T., Nemeth, J.M., Klein, E.G., Ferketich, A.K., Kwan, M. and Wewers, M.E. (2015) 'Risk Perceptions of Smokeless Tobacco Among Adolescent and Adult Users and Nonusers', *Journal of Health Communication,* 20(5), pp. 599-606. doi: 10.1080/10810730.2015.1012237.

Llewellyn, C.D., Johnson, N.W. and Warnakulasuriya, K. A. A. S (2001) *Risk factors for squamous cell carcinoma of the oral cavity in young people — a comprehensive literature review*, England: Elsevier Ltd.

Llewellyn, C.D., Linklater, K., Bell, J., Johnson, N.W. and Warnakulasuriya, S. (2004) 'An analysis of risk factors for oral cancer in young people: a case-control study', *Oral Oncology,* 40(3), pp. 304-313. doi: 10.1016/j.oraloncology.2003.08.015.

Loef, M. and Walach, H. (2015) 'How applicable are results of systematic reviews and meta-analyses of health behaviour maintenance? A critical evaluation', Public health (London), 129(4), pp. 377-384. doi: 10.1016/j.puhe.2015.01.014.

Longman, J M., Pritchard, C., McNeill, A., Csikar, J., and Croucher R.E. (2010) 'Accessibility of chewing tobacco products in England', *Journal of Public Health,* 32(3), pp. 372-378. doi: 10.1093/pubmed/fdq035.

Loyha, K., Vatanasapt, P., Promthet, S. and Parkin, D.M. (2012) 'Risk factors for oral cancer in northeast Thailand', *Asian Pacific journal of cancer prevention : APJCP,* 13(10), pp. 5087.

Luo, J., Ye, W., Zendehdel, K., Adami, J., Adami, H., Boffetta, P. and Nyrén, O. (2007) 'Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study', *Lancet (London, England),* 369(9578), pp. 2015-2020. doi: 10.1016/S0140-6736(07)60678-3.

Maasland, D.H.E., van den Brandt, P A, Kremer, B., Goldbohm, R.A. and Schouten, L.J. (2014) 'Alcohol consumption, cigarette smoking and the risk of subtypes of head-neck cancer: results from the Netherlands Cohort Study', *BMC Cancer,* 14(1), pp. 187. doi: 10.1186/1471-2407-14-187.

Maasland, D.H.E., van den Brandt, Piet A, Kremer, B., Goldbohm, R.A. and Schouten, L.J. (2015) 'Consumption of vegetables and fruits and risk of subtypes of head-neck cancer in the Netherlands Cohort Study', *International Journal of Cancer,* 136(5), pp. 396. doi: 10.1002/ijc.29219.

Madani, A.H., Dikshit, M. and Bhaduri, D. (2012) 'Risk for oral cancer associated to smoking, smokeless and oral dip products', *Indian Journal of Public Health,* 56(1), pp. 57. doi: 10.4103/0019-557X.96977.

Madathil, S.A., Rousseau, M., Wynant, W., Schlecht, N.F., Netuveli, G., Franco, E.L. and Nicolau, B. (2016) 'Nonlinear association between betel quid chewing and oral cancer: Implications for prevention', *Oral Oncology,* 60, pp. 25-31. doi: 10.1016/j.oraloncology.2016.06.011.

Mahapatra, S., Kamath, R., Shetty, B.K. and Binu, V.S. (2015) 'Risk of oral cancer associated with gutka and other tobacco products: a hospital-based case-control study', *Journal of cancer research and therapeutics,* 11(1), pp. 199-203. doi: 10.4103/0973-1482.143332.

Malhotra, S., Kakkar, N., Khan, I. and Ghosh, A. (2016) 'Smoking and Smokeless Tobacco Use in Children & Adolescents: Clinical Profile and Comparison', *Journal of Indian Association for Child & Adolescent Mental Health,* 12(2), pp. 121-141.

Malson, J.L., Sims, K., Murty, R. and Pickworth, W.B. (2001) 'Comparison of the nicotine content of tobacco used in bidis and conventional cigarettes', Tobacco Control, 10(2), pp. 181-183. doi: 10.1136/tc.10.2.181.

Mane, P. (1994) 'Exploration of Some Determinants of Lifestyles', *The Indian Journal of Social Work*, 55(1), pp. 13-24.

Mantler, T. (2013) 'A systematic review of smoking Youths' perceptions of addiction and health risks associated with smoking: Utilizing the framework of the health belief model', *Addiction Research & Theory,* 21(4), pp. 306-317. doi: 10.3109/16066359.2012.727505.

Marques, L.A., Eluf-Neto, J., Figueiredo, R.A.O., de Góis-Filho, J.F., Kowalski, L.P., de Carvalho, M.B., Abrahão, M. and Wünsch-Filho, V. (2008) 'Oral health, hygiene practices and oral cancer', *Revista de saúde pública,* 42(3), pp. 471-479. doi: 10.1590/S0034-89102008000300012.

Marron, M., Boffetta, P., Zhang, Z., Zaridze, D., Wünsch-Filho, V., Winn, D.M., Wei, Q., Talamini, R., Szeszenia-Dabrowska, N., Sturgis, E.M., Smith, E., Schwartz, S.M., Rudnai, P., Purdue, M.P., Olshan, A.F., Eluf-Neto, J., Muscat, J., Morgenstern, H., Menezes, A., McClean, M., Matos, E., Mates, I.N., Lissowska, J., Levi, F., Lazarus, P., Vecchia, C.L., Koifman, S., Kelsey, K., Herrero, R., Hayes, R.B., Franceschi, S., Fernandez, L., Fabianova, E., Daudt, A.W., Maso, L.D., Curado, M.P., Cadoni, G., Chen, C., Castellsague, X., Boccia, S., Benhamou, S., Ferro, G., Berthiller, J., Brennan, P., Møller, H. and Hashibe, M. (2010) 'Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk', *International Journal of Epidemiology,* 39(1), pp. 182-196. doi: 10.1093/ije/dyp291.

Mathur, C., Stigler, M.H., Perry, C.L., Arora, M. and Reddy, K.S. (2008) 'Differences in prevalence of tobacco use among Indian urban youth: the role of socioeconomic status', *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco,* 10(1), pp. 109-116. doi: 10.1080/14622200701767779.

Mathur, R., Singhavi, H.R., Malik, A., Nair, S. and Chaturvedi, P. (2019) 'Role of Poor Oral Hygiene in Causation of Oral Cancer-a Review of Literature', *Indian Journal of Surgical Oncology,* 10(1), pp. 184-195. doi: 10.1007/s13193-018-0836-5.

Mavropoulos, A., Aars, H. and Brodin, P. (2001) 'The acute effects of smokeless tobacco (snuff) on gingival blood flow in man', *Journal of periodontal research,* 36(4), pp. 221-226. doi: 10.1034/j.1600-0765.2001.036004221. x.

Mavropoulos, A., Aars, H. and Brodin, P. (2002) 'The involvement of nervous and some inflammatory response mechanisms in the acute snuff-induced gingival hyperaemia in humans', *Journal of clinical periodontology,* 29(9), pp. 855.

McAlister A L., Perry C L., Parcel G S. (2015) ‘Health Behavior and Health Education Theory, Research, and Practice in Glanz K., Rimer B K., and Viswanath. K (5th ED) *Health Behavior.* Fifth edit edn. New York, NY: Jossey Bass Ltd, pp. 159-183

Mehrotra, R., Gupta, A., Singh, M. and Ibrahim, R. (2012) 'Retraction: Application of cytology and molecular biology in diagnosing premalignant or malignant oral lesions', *Molecular Cancer,* 11(1), pp. 57. doi: 10.1186/1476-4598-11-57.

Mehrotra, R., Sinha, D. and Szilagyi, T. (2018) *Global smokeless tobacco control polices and their implementation, Executive Summary.* Available at: http://untobaccocontrol.org (Accessed: July 11, 2018).

Mehrotra, R., Yadav, A., Sinha, D.N., Parascandola, M., John, R.M., Ayo-Yusuf, O., Nargis, N., Hatsukami, D.K., Warnakulasuriya, S., Straif, K., Siddiqi, K. and Gupta, P.C. (2019) 'Smokeless tobacco control in 180 countries across the globe: call to action for full implementation of WHO FCTC measures', *The Lancet Oncology*, 20(4), pp. e208-e217. doi: 10.1016/S1470-2045(19)30084-1.

Melamed, A. and Robinson, J.N. (2019) 'Case-control studies can be useful but have many limitations: Study design: case-control studies', *BJOG : an international journal of obstetrics and gynaecology,* 126(1), pp. 23. doi: 10.1111/1471-0528.15200.

Merchant, A., Husain, S.S.M., Hosain, M., Fikree, F.F., Pitiphat, W., Siddiqui, A.R., Hayder, S.J., Haider, S.M., Ikram, M., Chuang, S. and Saeed, S.A. (2000) 'Paan without tobacco: An independent risk factor for oral cancer', *International Journal of Cancer,* 86(1), pp. 128-131. doi: AID-IJC20>3.0.CO;2-M.

Metgud, R., Murugesh, C.J., Shiva Kumar, B.N., Priya, N.K., Rashmi, P., Naik, S. and Tak, A. (2018) 'Prevalence, knowledge, and attitude of gutkha chewing among school children of Arsikere, India', *Journal of cancer research and therapeutics,* 14(2), pp. 368-371. doi: 10.4103/0973-1482.174532.

Mia, M.N., Hanifi, S.M.A., Rahman, M.S., Sultana, A., Hoque, S. and Bhuiya, A. (2017) 'Prevalence, pattern and sociodemographic differentials in smokeless tobacco consumption in Bangladesh: evidence from a population-based cross-sectional study in Chakaria', *BMJ Open,* 7(1). doi: 10.1136/bmjopen-2016-012765.

Mickey, R.M. and Greenland, S. (1989) 'The impact of confounder selection criteria on effect estimation', *American journal of epidemiology,* 129(1), pp. 125-137. doi: 10.1093/oxfordjournals.aje.a115101.

Mikkelsen, B., Williams, J., Rakovac, I., Wickramasinghe, K., Hennis, A., Shin, H., Farmer, M., Weber, M., Berdzuli, N., Borges, C., Huber, M. and Breda, J. (2019) 'Life course approach to prevention and control of non-communicable diseases', *The BMJ,* 364. doi: 10.1136/bmj.l257.

Ministry of Health and Family Welfare (2007) *National Strategic Plan of Action for Tobacco Control, 2007-2010*. Abailable at: https://www.researchgate.net/publication/325248857_National_strategic_plan_of_action_for_tobacco_control_2007-2010 (Accessed: Jun 15, 2018)

Mistry, R., Pednekar, M.S., McCarthy, W.J., Resnicow, K., Pimple, S.A., Hsieh, H., Mishra, G.A. and Gupta, P.C. (2018) 'Compliance with point-of-sale tobacco control policies and student tobacco use in Mumbai, India', *Tobacco Control,* , pp. 54290. doi: 10.1136/tobaccocontrol-2018-054290.

Mitra, D.K., Mistry, S.K., Afsana, K. and Rahman, M. (2018) 'Demographic, socio-economic and lifestyle determinants of under- and over-nutrition among Bangladeshi adult population: Results from a large cross-sectional study', *Journal of Epidemiology and Global Health,* . doi: 10.1016/j.jegh.2018.03.002.

Mohamed, S. and Janakiram, C. (2013) 'Periodontal status among tobacco users in Karnataka, India', Indian journal of public health, 57(2), pp. 105-108. doi: 10.4103/0019-557X.115006.

Mohammadi, S., Ghajari, H., Valizade, R., Ghaderi, N., Yousefi, F., Taymoori, P. and Nouri, B. (2017) 'Predictors of Smoking among the Secondary High School Boy Students Based on the Health Belief Model', *International Journal of Preventive Medicine*, 8. doi: 10.4103/ijpvm.IJPVM_264_16.

Moher, D., Liberati, A., Tetzlaff, J. and Altman, D.G. (2009) 'Reprint—Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement', Physical therapy, 89(9), pp. 873-880. doi: 10.1093/ptj/89.9.873.

Montén, U., Wennström, J.L. and Ramberg, P. (2006) 'Periodontal conditions in male adolescents using smokeless tobacco (moist snuff', *Journal of clinical periodontology,* 33(12), pp. 863-868. doi: 10.1111/j.1600-051X.2006.01005.x.

Moreno-López, L.A., Esparza-Gómez, G.C., González-Navarro, A., Cerero-Lapiedra, R., González-Hernández, M.J. and Domínguez-Rojas, V. (2000) 'Risk of oral cancer associated with tobacco smoking, alcohol consumption and oral hygiene: a case-control study in Madrid, Spain', *Oral Oncology,* 36(2), pp. 170-174. doi: 10.1016/S1368-8375(99)00084-6.

Morrell, H.E.R., Lapsley, D.K. and Halpern-Felsher, B.L. (2016) 'Subjective Invulnerability and Perceptions of Tobacco-Related Benefits Predict Adolescent Smoking Behavior', *The Journal of Early Adolescence,* 36(5), pp. 679-703. doi: 10.1177/0272431615578274.

Muwonge, R., Ramadas, K., Sankila, R., Thara, S., Thomas, G., Vinoda, J. and Sankaranarayanan, R. (2008) 'Role of tobacco smoking, chewing and alcohol drinking in the risk of oral cancer in Trivandrum, India: A nested case-control design using incident cancer cases', *Oral Oncology,* 44(5), pp. 446-454. doi: 10.1016/j.oraloncology.2007.06.002.

Nargis, M., Akther, S. and Akther, F. (2013) *Zarda and Gul: Smokeless Tobacco Products in Bangladesh.* Available at: ubinig.org/npdf/20_16.pdf (Accessed: July 11, 2018).

Nargis, N., Hussain, A K M G and Fong, G.T. (2014a) 'Smokeless tobacco product prices and taxation in Bangladesh: findings from the International Tobacco Control Survey', *Indian journal of cancer,* 51 Suppl 1, pp. S33.

Nargis, N., Thompson, M.E., Fong, G.T., Driezen, P., Hussain, A K M Ghulam, Ruthbah, U.H., Quah, A.C.K. and Abdullah, A.S. (2015) 'Prevalence and Patterns of Tobacco Use in Bangladesh from 2009 to 2012: Evidence from International Tobacco Control (ITC) Study', *PloS one,* 10(11), pp. e0141135. doi: 10.1371/journal.pone.0141135.

Nasher, A.T., Al-Hebshi, N., Al-Moayad, E. and Suleiman, A.M. (2014) 'Viral infection and oral habits as risk factors for oral squamous cell carcinoma in Yemen: a case-control study', *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology,* 118(5), pp. 572.e1. doi: 10.1016/j.oooo.2014.08.005.

NCI (2011) *NCI Dictionary of Cancer Terms*. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms (Accessed: July 15, 2017).

NCI and CDC (2014) *Smokeless tobacco and Public Health: A Global Perspectives.* Available at: https://cancercontrol.cancer.gov/brp/tcrb/global-perspective/Executive_Summary_SmokelessTobaccoAndPublicHealth.pdf (Accessed: July 12, 2017).

Nelson, D.E., Jarman, D.W., Rehm, J., Greenfield, T.K., Rey, G., Kerr, W.C., Miller, P., Shield, K.D., Ye, Y. and Naimi, T.S. (2013) 'Alcohol-attributable cancer deaths and years of potential life lost in the United States', *American journal of public health,* 103(4), pp. 641-648. doi: 10.2105/AJPH.2012.301199.

Neupane, B., Walter, S.D., Krueger, P. and Loeb, M. (2010) 'Community controls were preferred to hospital controls in a case–control study where the cases are derived from the hospital', *Journal of Clinical Epidemiology,* 63(8), pp. 926-931. doi: 10.1016/j.jclinepi.2009.11.006.

Nieto, A., Sánchez, M.J., Martínez, C., Castellsagué, X., Quintana, M.J., Bosch, X., Conde, M., Muñoz, N., Herrero, R. and Franceschi, S. (2003) 'Lifetime body mass index and risk of oral cavity and oropharyngeal cancer by smoking and drinking habits', *British Journal of Cancer,* 89(9), pp. 1667-1671. doi: 10.1038/sj.bjc.6601347.

Nilan, K., Raw, M., McKeever, T.M., Murray, R.L. and McNeill, A. (2017) 'Progress in implementation of WHO FCTC Article 14 and its guidelines: a survey of tobacco dependence treatment provision in 142 countries', *Addiction,* 112(11), pp. 2023-2031. doi: 10.1111/add.13903.

Norman, P. and Brain, K. (2005) 'An application of an extended health belief model to the prediction of breast self-examination among women with a family history of breast cancer', British Journal of Health Psychology, 10(1), pp. 1-16. doi: 10.1348/135910704X24752.

Notani, P.N. (1988) 'Role of alcohol in cancers of the upper alimentary tract: use of models in risk assessment', *Journal of Epidemiology and Community Health,* 42(2), pp. 187-192.

Oji, C. and Chukwuneke, F. (2012) 'Poor oral Hygiene may be the Sole Cause of Oral Cancer', *Journal of Maxillofacial and Oral Surgery,* 11(4), pp. 379-383. doi: 10.1007/s12663-012-0359-5.

Orji, R., Vassileva, J. and Mandryk, R. (2012) 'Towards an Effective Health Interventions Design: An Extension of the Health Belief Model', Online Journal of Public Health Informatics, 4(3). doi: 10.5210/ojphi.v4i3.4321.

Orr, I. (1933) 'Oral cancer in betel nut chewers in travancore: its ateology, pathology and treatment, *The Lancet*, 222(5741), pp. 575-580. doi: 10.1016/S0140-6736(01)18622-8.

Pakhale, S.S., Jayant, K. and v. Bhide, S. (1990) 'Chemical analysis of smoke of Indian cigarettes, bidis and other indigenous forms of smoking--levels of steam-volatile phenol, hydrogen cyanide and benzo(a)pyrene', *The Indian journal of chest diseases & allied sciences,* 32(2), pp. 75-81.

Palipudi, K., Rizwan, S., Sinha, D., Andes, L., Amarchand, R., Krishnan, A. and Asma, S. (2014) 'Prevalence and sociodemographic determinants of tobacco use in four countries of the World Health Organisation: South-East Asia region: Findings from the Global Adult Tobacco Survey', *Indian Journal of Cancer,* 51(5), pp. 24-32. doi: 10.4103/0019-509X.147446.

Pannucci, C.J. and Wilkins, E.G. (2010) 'Identifying and avoiding bias in research', *Plastic and reconstructive surgery,* 126(2), pp. 619-625. doi: 10.1097/PRS.0b013e3181de24bc.

Panwar, S.K., Ansari, S.M. and Mulla, S.K. (2012) 'Oral Precancerous Lesions in Tobacco Users Attending Dental Outdoor in Jhalawar District of Rajasthan', *National Journal of Community Medicine,* 3(3), pp. 502-505.

Park, E., McCoy, T.P., Erausquin, J.T. and Bartlett, R. (2018) 'Trajectories of risk behaviors across adolescence and young adulthood: The role of race and ethnicity', *Addictive Behaviours,* 76, pp. 1-7. doi: 10.1016/j.addbeh.2017.07.014.

Park, J., Han, K., Park, Y. and Ko, Y. (2016) 'Association between socioeconomic status and oral health behaviors: The 2008-2010 Korea national health and nutrition examination survey', *Experimental and Therapeutic Medicine,* 12(4), pp. 2657-2664. doi: 10.3892/etm.2016.3679.

Parker, M.A., Villanti, A.C., Quisenberry, A.J., Stanton, C.A., Doogan, N.J., Redner, R., Gaalema, D.E., Kurti, A.N., Nighbor, T., Roberts, M.E., Cepeda-Benito, A. and Higgins, S.T. (2018) 'Tobacco Product Harm Perceptions and New Use', *Pediatrics,* 142(6), pp. e20181505. doi: 10.1542/peds.2018-1505.

Parmar, G., Sangwan, P., Vashi, P., Kulkarni, P. and Kumar, S. (2008) 'Effect of chewing a mixture of areca nut and tobacco on periodontal tissues and oral hygiene status', *Journal of Oral Science*, 50(1), pp. 57-62. doi: 10.2334/josnusd.50.57.

Patel, D., Kassim, S. and Croucher, R. (2012) 'Tobacco promotion and availability in school neighborhoods in India: a cross-sectional study of their impact on adolescent tobacco use', Asian Pacific journal of cancer prevention : APJCP, 13(8), pp. 4173-4176. doi: 10.7314/APJCP.2012.13.8.4173.

Patel, K.R., Vajaria, B.N., Begum, R., Desai, A., Patel, J.B., Shah, F.D., Shukla, S.N. and Patel, P.S. (2014) 'Prevalence of high-risk human papillomavirus type 16 and 18 in oral and cervical cancers in population from Gujarat, West India', *Journal of Oral Pathology & Medicine: Official Publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology,* 43(4), pp. 293-297. doi: 10.1111/jop.12147.

Patel, V.D., Jadhav, K.B., Shah, V.S. and Gupta, N.D. (2017) 'Comparative assessment of salivary cotinine level and psychological dependence among tobacco users', Dental Research Journal, 14(2), pp. 125-130.

Pathare, S.M., Gerstung, M., Beerenwinkel, N., Schäffer, A.A., Kannan, S., Pai, P., Pathak, K.A., Borges, A.M. and Mahimkar, M.B. (2011) 'Clinicopathological and prognostic implications of genetic alterations in oral cancers', *Oncology Letters,* 2(3), pp. 445-451. doi: 10.3892/ol.2011.271.

Patil, P.B., Bathi, R. and Chaudhari, S. (2013) 'Prevalence of oral mucosal lesions in dental patients with tobacco smoking, chewing, and mixed habits: A cross-sectional study in South India', *Journal of Family & Community Medicine,* 20(2), pp. 130-135. doi: 10.4103/2230-8229.114777.

Pattanayak, R.D. and Pattanayak, S.K. (2011) 'Adolescent Tobacco Use and Role Model Influence: Interpreting it Right!', *Indian Journal of Community Medicine : Official Publication of Indian Association of Preventive & Social Medicine,* 36(3), pp. 241. doi: 10.4103/0970-0218.86532.

Patten, C.A., Koller, K.R., Flanagan, C.A., Day, G.E., Umans, J.G., Austin, M.A., Hopkins, S.E. and Boyer, B. (2018) 'Age of initiation of cigarette smoking and smokeless tobacco use among western Alaska Native people: Secondary analysis of the WATCH study', *Addictive Behaviors Reports,* 9, pp. 100143. doi: 10.1016/j.abrep.2018.100143.

Pearce, N. (2016) 'Analysis of matched case-control studies', *British Medical Journal,* 352(8046), pp. 316.

Pednekar, M.S., Gupta, P.C., Shukla, H.C. and Hebert, J.R. (2006) 'Association between tobacco use and body mass index in urban Indian population: implications for public health in India', *BMC public health,* 6(1), pp. 70. doi: 10.1186/1471-2458-6-70.

Pelucchi, C., Gallus, S., Garavello, W., Bosetti, C. and Vecchia, C.L. (2006) 'Cancer risk associated with alcohol and tobacco use: focus on upper aero-digestive tract and liver', *Alcohol Research & Health: The Journal of the National Institute on Alcohol Abuse and Alcoholism,* 29(3), pp. 193-198.

Peng, Q., Wang, Y., Quan, H., LI, Y. and Tang, Z. (2016) 'Oral verrucous carcinoma: From multifactorial etiology to diverse treatment regimens (Review)', *International Journal of Oncology,* 49(1), pp. 59-73. doi: 10.3892/ijo.2016.3501.

Perry, B.J., Zammit, A.P., Lewandowski, A.W., Bashford, J.J., Dragovic, A.S., Perry, E.J., Hayatbakhsh, R. and Perry, C.F.L. (2015) 'Sites of origin of oral cavity cancer in nonsmokers vs smokers: possible evidence of dental trauma carcinogenesis and its importance compared with human papillomavirus', *JAMA otolaryngology-- head & neck surgery,* 141(1), pp. 5-11. doi: 10.1001/jamaoto.2014.2620.

Persoskie, A., O'Brien, E.K., Nguyen, A.B. and Tworek, C. (2017) 'Measuring youth beliefs about the harms of e-cigarettes and smokeless tobacco compared to cigarettes', *Addictive Behaviours,* 70, pp. 7-13. doi: 10.1016/j.addbeh.2017.01.033.

Pesko, M.F. and Robarts, A.M.T. (2017) 'Adolescent Tobacco Use in Urban Versus Rural Areas of the United States: The Influence of Tobacco Control Policy Environments', *The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine,* 61(1), pp. 70-76. doi: 10.1016/j.jadohealth.2017.01.019.

Petti, S. (2009) 'Lifestyle risk factors for oral cancer', *Oral Oncology,* 45(4), pp. 340-350. doi: 10.1016/j.oraloncology.2008.05.018.

Petti, S., Masood, M. and Scully, C. (2013a) 'The Magnitude of Tobacco Smoking-Betel Quid Chewing-Alcohol Drinking Interaction Effect on Oral Cancer in South-East Asia. A Meta-Analysis of Observational Studies', *PLoS One,* 8(11), pp. e78999. doi: 10.1371/journal.pone.0078999.

Petti, S., Masood, M., Messano, G.A. and Scully, C. (2013b) 'Alcohol is not a risk factor for oral cancer in nonsmoking, betel quid non-chewing individuals. A meta-analysis update', *Annali di igiene : medicina preventiva e di comunità,* 25(1), pp. 3.

Pierce, J.P., Sargent, J.D., Portnoy, D.B., White, M., Noble, M., Kealey, S., Borek, N., Carusi, C., Choi, K., Green, V.R., Kaufman, A.R., Leas, E., Lewis, M.J., Margolis, K.A., Messer, K., Shi, Y., Silveira, M.L., Snyder, K., Stanton, C.A., Tanski, S.E., Bansal-Travers, M., Trinidad, D. and Hyland, A. (2018) 'Association Between Receptivity to Tobacco Advertising and Progression to Tobacco Use in Youth and Young Adults in the PATH Study', *JAMA pediatrics,* 172(5), pp. 444-451. doi: 10.1001/jamapediatrics.2017.5756.

Pintos, J., Black, M.J., Sadeghi, N., Ghadirian, P., Zeitouni, A.G., Viscidi, R.P., Herrero, R., Coutlée, F. and Franco, E.L. (2008) 'Human papillomavirus infection and oral cancer: a case-control study in Montreal, Canada', *Oral Oncology,* 44(3), pp. 242-250. doi: 10.1016/j.oraloncology.2007.02.005.

Plurphanswat, N. and Rodu, B. (2014) 'The association of smoking and demographic characteristics on body mass index and obesity among adults in the U.S., 1999-2012', *BMC obesity,* 1, pp. 18. doi: 10.1186/s40608-014-0018-0.

Poling, J.S., Ma, X., Bui, S., Luo, Y., Li, R., Koch, W.M. and Westra, W.H. (2014) 'Human papillomavirus (HPV) status of non-tobacco related squamous cell carcinomas of the lateral tongue', Oral oncology, 50(4), pp. 306-310. doi: 10.1016/j.oraloncology.2014.01.006.

Pollaers, K., Kujan, O., Johnson, N.W. and Farah, C.S. (2017) 'Oral and oropharyngeal cancer in Oceania', *Translational Research in Oral Oncology,* 2, pp. 2057178. doi: 10.1177/2057178X17726455.

Post, A., Gilljam, H., Rosendahl, I., Bremberg, S. and Galanti, M.R. (2010) 'Symptoms of nicotine dependence in a cohort of Swedish youths: a comparison between smokers, smokeless tobacco users and dual tobacco users', *Addiction,* 105(4), pp. 740-746. doi: 10.1111/j.1360-0443.2009.02852.x.

Post, A., Gilljam, H., Rosendahl, I., Meurling, L., Bremberg, S. and Galanti, M.R. (2005) 'Validity of self reports in a cohort of Swedish adolescent smokers and smokeless tobacco (snus) users', *Tobacco Control,* 14(2), pp. 114-117. doi: 10.1136/tc.2004.008789.

Pourhoseingholi, M.A., Baghestani, A.R. and Vahedi, M. (2012) 'How to control confounding effects by statistical analysis', *Gastroenterology and hepatology from bed to bench,* 5(2), pp. 79.

Prabhu, N.T., Warnakulasuriya, K., Gelbier, S. and Robinson, P.G. (2001) 'Betel quid chewing among Bangladeshi adolescents living in East London', *International Journal of Paediatric Dentistry,* 11(1), pp. 18-24. doi: 10.1046/j.1365-263x.2001.00235.x.

Pradhan, P.M.S., Niraula, S.R., Ghimire, A., Singh, S.B. and Pokharel, P.K. (2013) 'Tobacco use and associated factors among adolescent students in Dharan, Eastern Nepal: a cross-sectional questionnaire survey', *BMJ Open,* 3(2), pp. e002123. doi: 10.1136/bmjopen-2012-002123.

Purdue, M.P., Hashibe, M., Berthiller, J., et al,(2009) 'Type of Alcoholic Beverage and Risk of Head and Neck Cancer-A Pooled Analysis Within the INHANCE Consortium', *American Journal of Epidemiology,* 169(2), pp. 132-142. doi: 10.1093/aje/kwn306.

Quadri, M.F., Tadakamadla, S. and John, T. (2019) 'Smokeless tobacco and oral cancer in the Middle East and North Africa: A systematic review and meta-analysis', *Tobacco Induced Diseases,* 17(July), pp. 56. doi: 10.18332/tid/110259.

Quadri, M.F.A., Alharbi, F., Bajonaid, A.M.S., Moafa, I.H.Y., Sharwani, A.A. and Alamir, A.H.A. (2015) 'Oral squamous cell carcinoma and associated risk factors in Jazan, Saudi Arabia: a hospital based case control study', *Asian Pacific journal of cancer prevention : APJCP,* 16(10), pp. 4335-4338. doi: 10.7314/APJCP.2015.16.10.4335.

Radoï, L. and Luce, D. (2013) 'A review of risk factors for oral cavity cancer: the importance of a standardized case definition', *Community Dentistry and Oral Epidemiology,* 41(2), pp. 91. doi: 10.1111/j.1600-0528.2012.00710.x.

Radoï, L., Menvielle, G., Cyr, D., Lapôtre-Ledoux, B., Stücker, I. and Luce, D. (2015) 'Population attributable risks of oral cavity cancer to behavioral and medical risk factors in France: results of a large population-based case–control study, the ICARE study', *BMC cancer,* 15(826), pp. 827. doi: 10.1186/s12885-015-1841-5.

Radoï, L., Paget-Bailly, S., Cyr, D., Papadopoulos, A., Guida, F., Schmaus, A., Cénée, S., Menvielle, G., Carton, M., Lapôtre-Ledoux, B., Delafosse, P., Stücker, I. and Luce, D. (2013b) 'Tobacco smoking, alcohol drinking and risk of oral cavity cancer by subsite: results of a French population-based case-control study, the ICARE study', *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP),* 22(3), pp. 268-276. doi: 10.1097/CEJ.0b013e3283592cce.

Radoï, L., Paget-Bailly, S., Cyr, D., Papadopoulos, A., Guida, F., Tarnaud, C., Menvielle, G., Schmaus, A., Cénée, S., Carton, M., Lapôtre-Ledoux, B., Delafosse, P., Stücker, I. and Luce, D. (2013a) 'Body mass index, body mass change, and risk of oral cavity cancer: results of a large population-based case–control study, the ICARE study', *Cancer Causes & Control,* 24(7), pp. 1437-1448. doi: 10.1007/s10552-013-0223-z.

Radoï, L., Paget-Bailly, S., Guida, F., Cyr, D., Menvielle, G., Schmaus, A., Carton, M., Cénée, S., Sanchez, M., Guizard, A.V., Trétarre, B., Stücker, I. and Luce, D. (2013b) 'Family history of cancer, personal history of medical conditions and risk of oral cavity cancer in France: the ICARE study.', *BMC cancer,* 13, pp. 560. doi: 10.1186/1471-2407-13-560.

Rahman, M. and Fukui, T. (2000) 'Bidi smoking and health', *Public Health,* 114(2), pp. 123-127. doi: 10.1038/sj.ph.1900625.

Rahman, M., Sakamoto, J. and Fukui, T. (2003) 'Bidi smoking and oral cancer: A meta-analysis', *International Journal of Cancer,* 106(4), pp. 600-604. doi: 10.1002/ijc.11265.

Rahman, M.A. and Zaman, M.M. (2008) 'Smoking and smokeless tobacco consumption: Possible risk factors for coronary heart disease among young patients attending a tertiary care cardiac hospital in Bangladesh', *Public Health*, 122(12), pp. 1331-1338. doi: 10.1016/j.puhe.2008.05.015.

Rahman, M.A., Mahmood, M.A., Spurrier, N., Rahman, M., Choudhury, S.R. and Leeder, S. (2015) 'Why Do Bangladeshi People Use Smokeless Tobacco Products?', *Asia-Pacific Journal of Public Health,* 27(2), pp. NP2209. doi: 10.1177/1010539512446957.

Rahman, M.A., Spurrier, N., Mahmood, M.A., Rahman, M., Choudhury, S.R. and Leeder, S. (2011) 'SP2-2 Community controls vs hospital controls: choice for a case-control study in Bangladesh', *Journal of Epidemiology & Community Health,* 65(Suppl 1), pp. A406. doi: 10.1136/jech.2011.142976n.92.

Rahman, M.A., Spurrier, N., Mahmood, M.A., Rahman, M., Choudhury, S.R. and Leeder, S. (2012) 'Is There Any Association between Use of Smokeless Tobacco Products and Coronary Heart Disease in Bangladesh?', *PLoS One,* 7(1), pp. e30584. doi: 10.1371/journal.pone.0030584.

Rajkumar, T., Sridhar, H., Balaram, P., Vaccarella, S., Gajalakshmi, V., Nandakumar, A., Ramdas, K., Jayshree, R., Muñoz, N., Herrero, R., Franceschi, S. and Weiderpass, E. (2003) 'Oral cancer in Southern India: the influence of body size, diet, infections and sexual practices', *European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation (ECP),* 12(2), pp. 135-143. doi: 10.1097/01.cej.0000062796.86004.7c.

Randolph, C.C. (2017) 'Perceptions of e-Cigarettes and Noncigarette Tobacco Products Among US Youth', *Pediatrics,* 140(6), pp. S187.

Rantao, M. and Ayo-Yusuf, O.A. (2012) 'Dual use of cigarettes and smokeless tobacco among South African adolescents', *American Journal of Health Behaviour,* 36(1), pp. 124-133. doi: 10.5993/ajhb.36.1.13.

Rash, C. and Copeland, A. (2008) 'The Brief Smoking Consequences Questionnaire-Adult (BSCQ-A): Development of a short form of the SCQ-A', *Nicotine & Tobacco Research,* 10(11), pp. 1633-1643. doi: 10.1080/14622200802409990.

Reddy, K.S., Perry, C.L., Stigler, M.H. and Arora, M. (2006) 'Differences in tobacco use among young people in urban India by sex, socioeconomic status, age, and school grade: assessment of baseline survey data', *The Lancet,* 367(9510), pp. 589-594. doi: 10.1016/S0140-6736(06)68225-1.

Reddy, S., Prashanth, R., Yashodha Devi, B., Chugh, N., Kaur, A. and Thomas, N. (2015) 'Prevalence of oral mucosal lesions among chewing tobacco users: A cross-sectional study', Indian Journal of Dental Research, 26(5), pp. 537-541. doi: 10.4103/0970-9290.172083.

Rêgo, M.A.V. (2010) 'Case-control study: a brief review', *Gazeta Médica da Bahia,* 1(144).

Rehm, J. and Shield, K. (2013) 'Alcohol and Mortality: Global Alcohol-Attributable deaths From Cancer, Liver Cirrhosis, and Injury in 2010', *Alcohol Research,* 35(2), pp. 174.

Richter, P. and Spierto, F.W. (2003) 'Surveillance of smokeless tobacco nicotine, pH, moisture, and unprotonated nicotine content', *Nicotine & Tobacco Research,* 5(6), pp. 885-889. doi: 10.1080/14622200310001614647.

Rinchen, S., Taneepanichskul, S. and Dawa, N. (2018) 'Prevalence and predictors of tobacco use among Bhutanese adolescents', Journal of health research, 32(4), pp. 288-297. doi: 10.1108/JHR-05-2018-031.

Rinchen, S., Taneepanichskul, S. and Dawa, N. (2018), "Prevalence and predictors of tobacco use among Bhutanese adolescents", *Journal of Health Research*, 32(4), pp. 288-297. https://doi.org/10.1108/JHR-05-2018-031.

Rodgman, A. and Perfetti, T.A. (2016) *The Chemical Components of Tobacco and Tobacco Smoke.* CRC Press.

Roditis, M, Delucchi, K., Cash, D. and Halpern-Felsher, B, D. (2016) 'Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ Across Tobacco Products', *Journal of Adolescent Health,* 58(5), pp. 558-566. doi: 10.1016/j.jadohealth.2016.01.012.

Rodriguez, T., Altieri, A., Chatenoud, L., Gallus, S., Bosetti, C., Negri, E., Franceschi, S., Levi, F., Talamini, R. and La Vecchia, C. (2004) 'Risk factors for oral and pharyngeal cancer in young adults', *Oral Oncology,* 40(2), pp. 207-213. doi: 10.1016/j.oraloncology.2003.08.014.

Rodu, B. and Godshall, W.T. (2006) 'Tobacco harm reduction: an alternative cessation strategy for inveterate smokers', *Harm reduction journal,* 3(1), pp. 37. doi: 10.1186/1477-7517-3-37.

Rolandsson, M., Hellqvist, L., Lindqvist, L. and Hugoson, A. (2005) 'Effects of snuff on the oral health status of adolescent males: a comparative study', *Oral health & preventive dentistry,* 3(2), pp. 77.

Rose, M.L., Chadha, D. and Bhutia, T.D. (2016) 'Smokeless tobacco use and perceptions of risk among students in Mumbai municipal schools', *Indian Journal of Cancer,* 53(2), pp. 322. doi: 10.4103/0019-509X.197720.

Rosendahl, K.I., Galanti, M.R., Gilljam, H. and Ahlbom, A. (2003) 'Smoking mothers and snuffing fathers: behavioural influences on youth tobacco use in a Swedish cohort', *Tobacco Control,* 12(1), pp. 74-78. doi: 10.1136/tc.12.1.74.

Rosendahl, K.I., Galanti, M.R., Gilljam, H. and Ahlbom, A. (2005) 'Knowledge about tobacco and subsequent use of cigarettes and smokeless tobacco among Swedish adolescents', *Journal of Adolescent Health,* 37(3), pp. 224-228. doi: 10.1016/j.jadohealth.2004.08.021.

Rosenstock, I., Strecher, V. and Becker, M. (1988) 'Social Learning Theory and the Health Belief Model', *Health Education Quaterly*, 15(2), pp. 175-83.

Rothman, K.J., Greenland, S. and Lash, T.L. (2012) *Modern epidemiology.* 3. rev. ed edn. Philadelphia, PA [u.a.]: Lippincott, Williams & Wilkins [u.a.].

Rout, S.K. and Arora, M. (2014) 'Taxation of smokeless tobacco in India', *Indian journal of cancer,* 51 Suppl 1, pp. S12. doi: 10.4103/0019-509X.147420.

Rozi, S and Akhtar S. (2007) 'Prevalence and predictors of smokeless tobacco use among high-school males in Karachi, Pakistan', *Eastern Mediterranean Health Journal,* 13(4), pp. 916-924.

Rudatsikira, E., Muula, A.S. and Siziya, S. (2010) 'Current use of smokeless tobacco among adolescents in the Republic of Congo', *BMC public health,* 10(1), pp. 16. doi: 10.1186/1471-2458-10-16.

Sabnis, R., Sahu, K., Thakur, D., Surana, S., Mazhar, H. and Pandey, S. (2016) 'Urban and rural disparity in tobacco use and knowledge about oral cancer among adolescents: An epidemiological survey on 12 and 15-year school going students', *Journal of International Society of Preventive & Community Dentistry,* 6(Suppl 3), pp. S231. doi: 10.4103/2231-0762.197200.

Sand, L., Wallström, M. and Hirsch, J. (2014) 'Smokeless tobacco, viruses and oral cancer', *Oral health and dental management,* 13(2), pp. 372.

Sankaranarayanan, R., Duffy, S.W., Day, N.E., Nair, M.K. and Padmakumary, G. (1989) 'A case-control investigation of cancer of the oral tongue and the floor of the mouth in southern India', *International journal of cancer,* 44(4), pp. 617-621. doi: 10.1002/ijc.2910440410.

Sankaranarayanan, R., Duffy, S.W., Padmakumary, G., Day, N.E. and Nair, M.K. (1990) 'Risk factors for cancer of the buccal and labial mucosa in Kerala, southern India', *Journal of Epidemiology and Community Health,* 44(4), pp. 286-292.

Sankaranarayanan, R., Ramadas, K., Amarasinghe, H., Subramanian, S. and Johnson, N. (2015) 'Oral Cancer: Prevention, Early Detection, and Treatment', in Gelband, H., Jha, P., Sankaranarayanan, R. and Horton, S. (eds.) *Cancer: Disease Control Priorities, Third Edition (Volume 3)* Washington (DC): The International Bank for Reconstruction and Development / The World Bank.

Sansone, G. (2014) Acceptability of Female Smoking and Smokeless Tobacco Use in Bangladesh and India. University of Waterloo. Available at: http://hdl.handle.net/10012/8936 (Accessed: May, 19, 2019)

Sardana, M., Goel, S., Gupta, M., Sardana, V. and Singh, B.S. (2015) 'Is Exposure to Tobacco Advertising, Promotion and Sponsorship Associated with Initiation of Tobacco Use among Current Tobacco Users in Youth in India?', *Asian Pacific journal of cancer prevention: APJCP,* 16(15), pp. 6299-6302.

Sarker, M.N.I., Wu, M. and Hossin, M.A. (2019) 'Economic Effect of School Dropout in Bangladesh', International journal of information and education technology, 9(2), pp. 136-142. doi: 10.18178/ijiet.2019.9.2.1188.

Auluck, A., Hislop, G., Poh, C., Zhang, L. and Rosin, M.P. (2009) 'Areca nut and betel quid chewing among South Asian immigrants to Western countries and its implications for oral cancer screening', *Rural and remote health,* 9(2), pp. 1118.

Sawair, F.A., Al-Mutwakel, A., Al-Eryani, K., Al-Surhy, A., Maruyama, S., Cheng, J., Al-Sharabi, A. and Saku, T. (2007) 'High relative frequency of oral squamous cell carcinoma in Yemen: Qat and tobacco chewing as its aetiological background', *International Journal of Environmental Health Research,* 17(3), pp. 185-195. doi: 10.1080/09603120701254813.

Schantz, S.P. and Yu, G. (2002) 'Head and neck cancer incidence trends in young Americans, 1973-1997, with a special analysis for tongue cancer', *Archives of Otolaryngology--Head & Neck Surgery,* 128(3), pp. 268-274.

Schlecht, N.F., Franco, E.L., Pintos, J. and Kowalski, L.P. (1999) 'Effect of Smoking Cessation and Tobacco Type on the Risk of Cancers of the Upper Aero-Digestive Tract in Brazil', *Epidemiology,* 10(4), pp. 412-418. doi: 10.1097/00001648-199907000-00012.

Schlesselman, J.J. and Stolley, P.D. (1982) Case control studies. New York: Oxford University Press.

Severson, H.H., Forrester, K.K. and Biglan, A. (2007) 'Use of smokeless tobacco is a risk factor for cigarette smoking', *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco,* 9(12), pp. 1331-1337. doi: 10.1080/14622200701705209.

Shahjahan, M., Harun, M.G.D., Chowdhury, A B M Alauddin, Ahmed, K. and Khan, H.T.A. (2017) 'Factors Influencing the Initiation of Smokeless Tobacco Consumption Among Low Socioeconomic Community in Bangladesh: A Qualitative Investigation', *International Quarterly of Community Health Education,* 37(3-4), pp. 181-187. doi: 10.1177/0272684X17736244.

Shaikh, M.H., Khan, A.I., Sadat, A., Chowdhury, A.H., Jinnah, S.A., Gopalan, V., Lam, A.K., Clarke, D.T.W., McMillan, N.A.J. and Johnson, N.W. (2017) 'Prevalence and types of high-risk human papilloma viruses in head and neck cancers from Bangladesh', *BMC Cancer,* 17(1). doi: 10.1186/s12885-017-3789-0.

Sharma, A. (2017) 'Global research priorities for noncommunicable diseases prevention, management, and control', *International Journal of Noncommunicable Diseases*, 2(4), pp. 107-112. doi: 10.4103/jncd.jncd_57_17.

Sharma, P., Wadhwan, V., Aggarwal, P. and Sharma, N. (2017) 'Adolescent tobacco menace: Attitudes, norms, and parental influence', *Indian journal of dental research,* 28(4), pp. 465.

Sharma, R., Grover, V.L. and Chaturvedi, S. (2010) 'Tobacco use among adolescent students and the influence of role models', *Indian Journal of Community Medicine: Official Publication of Indian Association of Preventive & Social Medicine,* 35(2), pp. 272-275. doi: 10.4103/0970-0218.66891.

Sharma, S., Mishra, S.K. and Mittal, N. (2018) 'Influence of tobacco dependence on caries development in young male adults: A cross-sectional study', Journal of Conservative Dentistry : JCD, 21(6), pp. 597-601. doi: 10.4103/JCD.JCD_218_18.

Shield, K.D., Ferlay, J., Jemal, A., Sankaranarayanan, R., Chaturvedi, A.K., Bray, F. and Soerjomataram, I. (2017) 'The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012', *CA: A Cancer Journal for Clinicians,* 67(1), pp. 51-64. doi: 10.3322/caac.21384.

Shield, K.D., Rylett, M., Gmel, G., Gmel, G., Kehoe-Chan, T.A.K. and Rehm, J. (2013) 'Global alcohol exposure estimates by country, territory and region for 2005--a contribution to the Comparative Risk Assessment for the 2010 Global Burden of Disease Study', *Addiction (Abingdon, England),* 108(5), pp. 912-922. doi: 10.1111/add.12112.

Shohel, M.M.C. (2014) 'Impact of Childhood Poverty on Education for Disadvantaged Children in Bangladesh', Child studies in Asia-Pacific contexts, 4(2), pp. 77-94.

Shrivastava, N., Verma, N., Bhawnani, D. and Soni, G. (2015) 'Prevalence of smokeless tobacco use among school going adolescent students of Raipur city Chhattisgarh state, India', International journal of research in medical sciences, 3(4), pp. 921. doi: 10.5455/2320-6012.ijrms20150420.

Siddiqi, K., Dogar, O., Rashid, R., Jackson, C., Kellar, I., O'Neill, N., Hassan, M., Ahmed, F., Irfan, M., Thomson, H. and Khan, J. (2016b) 'Behaviour change intervention for smokeless tobacco cessation: its development, feasibility and fidelity testing in Pakistan and in the UK', *BMC Public Health,* 16(1), pp. 1-15. doi: 10.1186/s12889-016-3177-8.

Siddiqi, K., Husain, S., Vidyasagaran, A., Readshaw, A., Mishu, M.P. and Sheikh, A. (2020) 'Global burden of disease due to smokeless tobacco consumption in adults: an updated analysis of data from 127 countries', BMC medicine, 18(1), pp. 1-222. doi: 10.1186/s12916-020-01677-9.

Siddiqi, K., Scammell, K., Huque, R., Khan, A., Baral, S., Ali, S. and Watt, I. (2016) 'Smokeless Tobacco Supply Chain in South Asia: A Comparative Analysis Using the WHO Framework Convention on Tobacco Control', *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 18(4), pp. 424-430. doi: 10.1093/ntr/ntv067.

Siddiqi, K., Shah, S., Abbas, S.M., Vidyasagaran, A., Jawad, M., Dogar, O. and Sheikh, A. (2015) 'Global burden of disease due to smokeless tobacco consumption in adults: analysis of data from 113 countries', *BMC Medicine,* 13, pp. 194. doi: 10.1186/s12916-015-0424-2.

Siddiqi, K., Vidyasagaran, A., Readshaw, A. and Croucher, R. (2017) 'A Policy Perspective on the Global Use of Smokeless Tobacco', *Current Addiction Reports,* 4(4), pp. 503-510. doi: 10.1007/s40429-017-0166-7.

Siegel, R.L., Miller, K.D. and Jemal, A. (2015) 'Cancer statistics, 2015', *CA: A Cancer Journal for Clinicians,* 65(1), pp. 5-29. doi: 10.3322/caac.21254.

Silva, I. (1999) *Cancer epidemiology: principles and methods .* Lyon: Internet Agency for Research on Cancer.

Singh, S., Vijayakumar, N., Priyadarshini, H. and Jain, M. (2015) 'Tobacco use among high school children in Bangalore, India: A study of knowledge, attitude and practice', *Indian Journal of Cancer,* 52(4), pp. 690-693. doi: 10.4103/0019-509X.178413.

Singhvi, H.R., Malik, A. and Chaturvedi, P. (2017) 'The Role of Chronic Mucosal Trauma in Oral Cancer: A Review of Literature', *Indian Journal of Medical and Paediatric Oncology : Official Journal of Indian Society of Medical & Paediatric Oncology,* 38(1), pp. 44-50. doi: 10.4103/0971-5851.203510.

Sinha, D., Gupta, P., Ray, C. and Singh, P. (2012) 'Prevalence of smokeless tobacco use among adults in WHO South-East Asia', *Indian Journal of Cancer*, 49(4), pp. 342-346. doi: 10.4103/0019-509X.107726.

Sinha, D., Gupta, P.C., Parascondola, M., Kumar, A. and Mehrotra, R. (2018a) 'Global burden of smokeless tobacco (SLT) use', *Tobacco Induced Diseases,* 16(1). doi: 10.18332/tid/84444.

Sinha, D.N., Abdulkader, R.S. and Gupta, P.C. (2016) 'Smokeless tobacco-associated cancers: A systematic review and meta-analysis of Indian studies', *International Journal of Cancer,* 138(6), pp. 1368-1379. doi: 10.1002/ijc.29884.

Sinha, D.N., Gupta, P.C., Kumar, A., Bhartiya, D., Agarwal, N., Sharma, S., Singh, H., Parascandola, M. and Mehrotra, R. (2018b) 'The Poorest of Poor Suffer the Greatest Burden From Smokeless Tobacco Use: A Study From 140 Countries', *Nicotine & Tobacco Research,* 20(12), pp. 1529-1532. doi: 10.1093/ntr/ntx276.

Sinha, D.N., Kumar, A., Bhartiya, D., Sharma, S., Gupta, P.C., Singh, H. and Mehrotra, R. (2017) 'Smokeless Tobacco Use Among Adolescents in Global Perspective', *Nicotine & Tobacco Research,* 19(11), pp. 1395-1396. doi: 10.1093/ntr/ntx004.

Sinha, D.N., Palipudi, K.M., Jones, C.K., Khadka, B.B., Silva, P.D., Mumthaz, M., Shein, N.N.N., Gyeltshen, T., Nahar, K., Asma, S. and Kyaing, N.N. (2014) 'Levels and trends of smokeless tobacco use among youth in countries of the World Health Organisation South-East Asia Region', *Indian Journal of Cancer,* 51(5), pp. 50-53. doi: 10.4103/0019-509X.147472.

Sinha, D.N., Rizwan, S.A., Aryal, K.K., Karki, K.B., Zaman, M.M. and Gupta, P.C. (2015) 'Trends of Smokeless Tobacco use among Adults (Aged 15-49 Years) in Bangladesh, India and Nepal', *Asian Pacific journal of cancer prevention : APJCP,* 16(15), pp. 6561-6568. doi: 10.7314/APJCP.2015.16.15.6561.

Sinha, D.N., Suliankatchi, R.A., Gupta, P.C., Thamarangsi, T., Agarwal, N., Parascandola, M. and Mehrotra, R. (2018) 'Global burden of all-cause and cause-specific mortality due to smokeless tobacco use: systematic review and meta-analysis', *Tobacco Control,* 27(1), pp. 35-42. doi: 10.1136/tobaccocontrol-2016-053302.

Smith, M.L., Colwell, B., Forté, C.A., Pulczinski, J.C. and McKyer, E.L.J. (2015) 'Psychosocial Correlates of Smokeless Tobacco Use Among Indiana Adolescents', *Journal of community health,* 40(2), pp. 208-214. doi: 10.1007/s10900-014-9918-7.

Sobhan, S.M., Choudhury, S.R. and Chowdhury, I. (2015) 'Regional Variation of Tobacco Use in Bangladesh', *International Journal of Epidemiology*, 44(suppl_1), pp. i276. doi: 10.1093/ije/dyv096.534.

Somatunga, L.C., Sinha, D.N., Sumanasekera, P., Galapatti, K., Rinchen, S., Kahandaliyanage, A., Mehta, F.R. and Lanka, J.D.N. (2012) 'Smokeless tobacco use in Sri Lanka', *Indian journal of cancer,* 49(4), pp. 357-363. doi: 10.4103/0019-509X.107729.

Song, J.W. and Chung, K.C. (2010) 'Observational studies: cohort and case-control studies', *Plastic and reconstructive surgery,* 126(6), pp. 2234-2242. doi: 10.1097/PRS.0b013e3181f44abc.

Song, M., Marian, C., Brasky, T.M., Reisinger, S., Djordjevic, M. and Shields, P.G. (2016) 'Chemical and toxicological characteristics of conventional and low-TSNA moist snuff tobacco products', *Toxicology Letters,* 245, pp. 68-77. doi: 10.1016/j.toxlet.2016.01.012.

Souza, F.D.O., Miranda, S.S., Valente, A.L.P., Araújo, T.M.D. and Smolen, J.R. (2016) 'Bias in case - Control studies: Can it be avoided?', *Revista de Epidemiologia e Controle de Infecção,* 6(2). doi: 10.17058/reci.v6i2.6370.

Sreeramareddy, C T (1), Pradhan, P M S (2), Mir, I A (3) and Sin, S (4) (2014b) 'Smoking and smokeless tobacco use in nine South and Southeast Asian countries: Prevalence estimates and social determinants from Demographic and Health Surveys', *Population Health Metrics,* 12(1). doi: 10.1186/s12963-014-0022-0.

Sreeramareddy, C.T., Pradhan, P.M. and Sin, S. (2014a) 'Prevalence, distribution, and social determinants of tobacco use in 30 sub-Saharan African countries', *BMC Medicine,* 12, pp. 243. doi: 10.1186/s12916-014-0243-x.

Stacy, R.D. (1987) 'Instrument Evaluation Guides for Survey Research in Health Education and Health Promotion', Health education (Washington, D.C. 1975), 18(5), pp. 65-67. doi: 10.1080/00970050.1987.10614519.

Stanfill, S.B., Croucher, R.E., Gupta, P.C., Lisko, J.G., Lawler, T.S., Kuklenyik, P., Dahiya, M., Duncan, B., Kimbrell, J.B., Peuchen, E.H. and Watson, C.H. (2018) 'Chemical characterization of smokeless tobacco products from South Asia: Nicotine, unprotonated nicotine, tobacco-specific N′-Nitrosamines, and flavor compounds', *Food and Chemical Toxicology,* 118, pp. 626-634. doi: 10.1016/j.fct.2018.05.004.

Stefani, E., Boffetta, P., Deneo-Pellegrini, H., Ronco, A.L., Acosta, G., Ferro, G., Oreggia, F. and Leiva, J. (2006) 'The effect of smoking and drinking in oral and pharyngeal cancers: A case-control study in Uruguay', *Cancer Letters,* 246(1), pp. 282-289. doi: 10.1016/j.canlet.2006.03.008.

Stefani, E.D., Boffetta, P., Oreggia, F., Mendilaharsu, M. and Deneo-Pellegrini, H. (1998) 'Smoking patterns and cancer of the oral cavity and pharynx: a case–control study in Uruguay', *Oral Oncology,* 34(5), pp. 340-346. doi: 10.1016/S1368-8375(98)00014-1.

Stepanov, I., Hecht, S.S., Ramakrishnan, S. and Gupta, P.C. (2005) 'Tobacco-specific nitrosamines in smokeless tobacco products marketed in India', *International Journal of Cancer,* 116(1), pp. 16-19. doi: 10.1002/ijc.20966.

Streiner, D.L. and Norman, G.R. (2009) *PDQ Epidemiology (3rd Edition).* 3rd edn. Shelton, UNITED STATES: PMPH USA, Ltd.

Subady, B.N., Assanangkornchai, S. and Chongsuvivatwong, V. (2013) 'Prevalence, patterns and predictors of alcohol consumption in a mountainous district of Bhutan', *Drug and Alcohol Review,* 32(4), pp. 435-442. doi: 10.1111/dar.12015.

Subapriya, R., Thangavelu, A., Mathavan, B., Ramachandran, C.R. and Nagini, S. (2007) 'Assessment of risk factors for oral squamous cell carcinoma in Chidambaram, Southern India: a case-control study', *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP),* 16(3), pp. 251-256. doi: 10.1097/01.cej.0000228402.53106.9e.

Sumanth, S., Bhat, K.M. and Bhat, G.S. (2008) 'Periodontal health status in pan chewers with or without the use of tobacco', *Oral health & preventive dentistry*, 6(3), pp. 223.

Svedberg, P., Nygren, J.M., Staland-Nyman, C. and Nyholm, M. (2016) 'The validity of socioeconomic status measures among adolescents based on self-reported information about parents occupations, FAS and perceived SES; implication for health related quality of life studies', *BMC medical research methodology,* 16(1), pp. 48. doi: 10.1186/s12874-016-0148-9.

Szklo, M. and Nieto, F. (2014) *Epidemiology:: Beyond the Basics.* 3rd edn. New York: Jones & Bartlett Learning.

Tam, J., Day, H.R., Rostron, B.L. and Apelberg, B.J. (2015) 'A systematic review of transitions between cigarette and smokeless tobacco product use in the United States', *BMC public health,* 15(1), pp. 258. doi: 10.1186/s12889-015-1594-8.

Tapia, J. and Goldberg, L. (2011) 'The Challenges of Defining Oral Cancer: Analysis of an Ontological Approach', *Head and Neck Pathology*, 5(4), pp. 376-384. doi: 10.1007/s12105-011-0300-0.

Tareg, A.R.C., Modeste, N.N., Lee, J.W. and Santos, H.D. (2015) 'Health Beliefs About Tobacco With Betel Nut Use Among Adults in Yap, Micronesia', *International Quarterly of Community Health Education,* 35(3), pp. 245-257. doi: 10.1177/0272684X15581344.

Tenny, S. and Hoffman, M.R. (2020) 'Case Control Studies'*StatPearls* Treasure Island (FL): StatPearls Publishing.

Thakur, J.S., Prinja, S., Bhatnagar, N., Rana, S.K., Sinha, D.N. and Singh, P.K. (2015) 'Widespread inequalities in smoking & smokeless tobacco consumption across wealth quintiles in States of India: Need for targeted interventions', *The Indian Journal of Medical Research,* 141(6), pp. 789-798. doi: 10.4103/0971-5916.160704.

ThekkePurakkal, A.S., Naimi, A.I., Madathil, S.A., Puthiyannal, S.H.K., Netuveli, G., Sacker, A., Schlecht, N.F. and Nicolau, B. (2018) 'Differential impact of socioeconomic position across life on oral cancer risk in Kerala, India: An investigation of life-course models under a time-varying framework', *Community Dentistry and Oral Epidemiology,* 46(6), pp. 592-600. doi: 10.1111/cdoe.12404.

Thomas, S. and Kearsley, J. (1993) 'Betel quid and oral cancer: A review', *European Journal of Cancer Part B: Oral Oncology,* 29(4), pp. 251-255. doi: 10.1016/0964-1955(93)90044-F.

Thomas, S.J., Bain, C.J., Battistutta, D., Ness, A.R., Paissat, D. and Maclennan, R. (2007) 'Betel quid not containing tobacco and oral cancer: a report on a case-control study in Papua New Guinea and a meta-analysis of current evidence', *International journal of cancer,* 120(6), pp. 1318-1323. doi: 10.1002/ijc.22304.

Timberlake, D.S. (2016) 'Advertising Receptivity and Youth Initiation of Smokeless Tobacco', *Substance Use & Misuse,* 51(9), pp. 1077-1082. doi: 10.3109/10826084.2016.1160115.

Tomar, S.L. (2003) 'Is use of smokeless tobacco a risk factor for cigarette smoking? The U.S. experience', *Nicotine & Tobacco Research,* 5(4), pp. 561-569. doi: 10.1080/1462220031000118667.

Tomar, S.L. and Giovino, G.A. (1998) 'Incidence and predictors of smokeless tobacco use among US youth', *American Journal of Public Health,* 88(1), pp. 20-26. doi: 10.2105/AJPH.88.1.20.

Tomar, S.L., Winn, D.M., Swango, P.A., Giovino, G.A. and Kleinman, D.V. (1997) 'Oral mucosal smokeless tobacco lesions among adolescents in the United States', *Journal of Dental Research,* 76(6), pp. 1277-1286. doi: 10.1177/00220345970760060701.

Tripathy, J.P. (2018) 'Research priorities in non-communicable diseases in developing countries: time to go beyond prevalence studies', *Public health action,* 8(2), pp. 98-99. doi: 10.5588/pha.18.0023.

Turati, F., Edefonti, V., Bosetti, C., Ferraroni, M., Malvezzi, M., Franceschi, S., Talamini, R., Montella, M., Levi, F., Maso, L.D., Serraino, D., Polesel, J., Negri, E., Decarli, A. and Vecchia, C.L. (2013) 'Family history of cancer and the risk of cancer: a network of case–control studies', *Annals of Oncology,* 24(10), pp. 2651-2656. doi: 10.1093/annonc/mdt280.

Turati, F., Garavello, W., Tramacere, I., Pelucchi, C., Galeone, C., Bagnardi, V., Corrao, G., Islami, F., Fedirko, V., Boffetta, P., Vecchia, C.L. and Negri, E. (2013) 'A meta-analysis of alcohol drinking and oral and pharyngeal cancers: results from subgroup analyses', *Alcohol and alcoholism (Oxford, Oxfordshire),* 48(1), pp. 107-118. doi: 10.1093/alcalc/ags100.

US Department of Health Services (2012) *Social, Environmental, Cognitive, and Genetic Influences on the Use of Tobacco Among Youth.* Centers for Disease Control and Prevention (US).

Valladolid-López, M.d.C., Barrientos-Gutiérrez, T., Reynales-Shigematsu, L.M., Thrasher, J.F., Peláez-Ballestas, I., Lazcano-Ponce, E. and Hernández-Ávila, M. (2015) 'Evaluating the validity of self-reported smoking in Mexican adolescents', *BMJ Open*, 5(10), pp. e007485. doi: 10.1136/bmjopen-2014-007485.

Veeranki, S.P., Mamudu, H.M., John, R.M. and Ouma, A.E.O. (2015) 'Prevalence and correlates of tobacco use among school-going adolescents in Madagascar', *Journal of Epidemiology and Global Health,* 5(3), pp. 239-247. doi: 10.1016/j.jegh.2014.12.005.

Viner, R.M., Ozer, E.M., Denny, S., Marmot, M., Resnick, M., Fatusi, A. and Currie, C. (2012) 'Adolescence and the social determinants of health', *Lancet* (London, England), 379(9826), pp. 1641-1652. doi: 10.1016/S0140-6736(12)60149-4.

Vitalstrategies (2016) Bangladesh: People Behind the Packs - Oral Cancer. Available at: https://www.vitalstrategies.org/resources/bangladesh-people-behind-the-packs-oral-cancer/ (Accessed: May 1, 2020).

Vyas, T., Verma, P., Abidullah, M., Kushwaha, S.S., Sahoo, P.K., Priyadarshini, S.R., Subudhi, S.K. and Rana, V. (2018) 'Quantitative analysis of AgNOR counts and pap stain in exfoliative cytology specimens of oral mucosa in bidi smokers and nonsmokers', *Annals of African Medicine,* 17(4), pp. 210. doi: 10.4103/aam.aam_69_17.

Wacholder, S., Silverman, D.T., McLaughlin, J.K. and Mandel, J.S. (1992) 'Selection of controls in case-control studies. II. Types of controls', *American journal of epidemiology,* 135(9), pp. 1029-1041. doi: 10.1093/oxfordjournals.aje.a116397.

Walker, M.W., Evans, S.A., Wimpy, C., Berger, A.T. and Smith, A.A. (2018) 'Developing Smokeless Tobacco Prevention Messaging for At-Risk Youth: Early Lessons from "The Real Cost" Smokeless Campaign', *Health Equity,* 2(1), pp. 167-173. doi: 10.1089/heq.2018.0029.

Wang, X., Xu, J., Wang, L., Liu, C. and Wang, H. (2015) 'The role of cigarette smoking and alcohol consumption in the differentiation of oral squamous cell carcinoma for the males in China', *Journal of Cancer Research and Therapeutics*, 11(1), pp. 141-145. doi: 10.4103/0973-1482.137981.

Wardle, J., Jarvis, M.J., Steggles, N., Sutton, S., Williamson, S., Farrimond, H., Cartwright, M. and Simon, A.E. (2003) 'Socioeconomic disparities in cancer-risk behaviors in adolescence: baseline results from the Health and Behaviour in Teenagers Study (HABITS)', *Preventive Medicine,* 36(6), pp. 721-730.

Warnakulasuriya, S. (2005) 'Bidi smokers at increased risk of oral cancer', *Evidence-Based Dentistry,* 6(1), pp. 19. doi: 10.1038/sj.ebd.6400297.

Warnakulasuriya, S. (2008) 'Global epidemiology of oral and oropharyngeal cancer', *Oral Oncology,* 45(4), pp. 309-316. doi: 10.1016/j.oraloncology.2008.06.002.

Warnakulasuriya, S. (2009) 'Causes of oral cancer - an appraisal of controversies', *BDJ*, 207(10), pp. 471-475. doi: 10.1038/sj.bdj.2009.1009.

Warnakulasuriya, S., Sutherland, G. and Scully, C. (2005) 'Tobacco, oral cancer, and treatment of dependence', *Oral Oncology,* 41(3), pp. 244-260. doi: 10.1016/j.oraloncology.2004.08.010.

Warnakulasuriya, S., Trivedy, C. and Peters, T.J. (2002) 'Areca Nut Use: An Independent Risk Factor For Oral Cancer: The Health Problem Is Under-Recognised', *BMJ: British Medical Journal,* 324(7341), pp. 799-800.

Warren, J.C., Smalley, K.B. and Barefoot, K.N. (2015) 'Perceived ease of access to alcohol, tobacco and other substances in rural and urban US students', *Rural and remote health,* 15(4), pp. 3397.

Warren, J.C., Smalley, K.B. and Barefoot, K.N. (2017) 'Recent Alcohol, Tobacco, and Substance Use Variations Between Rural and Urban Middle and High School Students', *Journal of Child & Adolescent Substance Abuse,* 26(1), pp. 60-65. doi: 10.1080/1067828X.2016.1210550.

Weinberger, M., Greene, J.Y., Mamlin, J.J. and Jerin, M.J. (1981) 'Health beliefs and smoking behavior', *American Journal of Public Health,* 71(11), pp. 1253-1255. doi: 10.2105/AJPH.71.11.1253.

Weintraub, J.A. and Burt, B.A. (1987) 'Periodontal Effects and Dental Caries Associated with Smokeless Tobacco Use', *Public Health Reports (1974-),* 102(1), pp. 30-35.

Weitkunat, R., Sanders, E. and Lee, P.N. (2007) 'Meta-analysis of the relation between European and American smokeless tobacco and oral cancer', *BMC public health,* 7(1), pp. 334. doi: 10.1186/1471-2458-7-334.

Wellman, R.J., Dugas, E.N., Dutczak, H., O'Loughlin, E.K., Datta, G.D., Lauzon, B. and O'Loughlin, J. (2016) 'Predictors of the Onset of Cigarette Smoking: A Systematic Review of Longitudinal Population-Based Studies in Youth', *American journal of preventive medicine,* 51(5), pp. 767-778. doi: 10.1016/j.amepre.2016.04.003.

Wen, C.P., Tsai, M.K., Chung, W.S.I., Hsu, H.L., Chang, Y.C., Chan, H.T., Chiang, P.H., Cheng, T.D. and Tsai, S.P. (2010) 'Cancer risks from betel quid chewing beyond oral cancer: a multiple-site carcinogen when acting with smoking', *Cancer Causes & Control,* 21(9), pp. 1427-1435. doi: 10.1007/s10552-010-9570-1.

White, T.J., Redner, R., Bunn, J.Y. and Higgins, S.T. (2016) 'Do Socioeconomic Risk Factors for Cigarette Smoking Extend to Smokeless Tobacco Use?', *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco,* 18(5), pp. 869-873. doi: 10.1093/ntr/ntv199.

Whitney, C.W., Lind, B.K. and Wahl, P.W. (1998) 'Quality assurance and quality control in longitudinal studies', *Epidemiologic reviews*, 20(1), pp. 71-80. doi: 10.1093/oxfordjournals.epirev.a017973.

WHO (2003) *WHO framework convention on tobacco control*. Available at: https://www.who.int/tobacco/framework/WHO_FCTC_english.pdf (Accessed: Apr 10, 2018).

WHO (2008) *WHO Report on the Global Tobacco Epidemic 2008 : The MPOWER Package.* Albany: World Health Organisation.

WHO (2013a) *Global action plan for the prevention and control of noncommunicable diseases 2013-2020* World Health Organisation.

WHO (2013b) *WHO | Bangladesh – National tobacco control law amended*. Available at: https://www.who.int/fctc/implementation/news/news_ban/en/#:~:text=May%202013%20%2D%20The%20National%20Assembly,use%20some%20form%20of%20tobacco. [Accessed: March 23, 2015]

WHO (2014a) Global status report on alcohol and health 2014. Available at: https://apps.who.int/iris/bitstream/handle/10665/112736/9789240692763_eng.pdf?sequence=1 (Accessed: May 14, 2015)

WHO (2014b) International statistical classification of diseases and related health problems. Available at: https://icd.who.int/browse10/2019/en#/C00-C14 (Accessed: May 18, 2015)

WHO (2015) World Health Organisation, Tobacco control in Bangladesh. Available at: http://www.searo.who.int/bangladesh/tobacco-control/en/ (Accessed: May 1, 2020).

WHO (2016) *Malignant neoplasms of lip, oral cavity and pharynx.* Available at: https://icd.who.int/browse10/2010/en#/C00-C97 (Accessed: March 14, 2017)

WHO (2017) *Global adult tobacco survey: Fact Sheet, Bangladesh 2017.* Available at: http://bbs.portal.gov.bd (Accessed: Apr 12, 2019).

WHO (2018a) *WHO global report on trends in prevalence of tobacco smoking 2000-2025.* Available at: http://www.who.int/tobacco/publications/surveillance/trends-tobacco-smoking-second-edition/en/ (Accessed:Jun 19, 2019)

WHO (2018b) *Non-communicable diseases: Fact sheet (Updated January 2015). Geneva: World Health Organisation; 2015*.

WHO (2018c) Global Adult Tobacco Survey INDIA 2016-17. [online] WHO. Available at: https://ntcp.nhp.gov.in/assets/document/surveys-reports-publications/Global-Adult-Tobacco-Survey-Second-Round-India-2016-2017.pdf [Accessed: 13 May 2020].

WHO (2019) *World Health Organisation, Tobacco control in Bangladesh.* Available at: http://www.searo.who.int/bangladesh/tobacco-control/en/ (Accessed: Jun 16, 2019).

WHO, Regional Office for South-East Asia (2009) *Global adult tobacco survey: Bangladesh report 2009*.

WHO, Regional Office for South-East Asia (2015a) *Global Youth Tobacco Survey (GYTS), Bangladesh Report, 2013*.

Wiener, R.C. (2013) 'Association of smokeless tobacco use and smoking in adolescents in the United States: an analysis of data from the Youth Risk Behavior Surveillance System survey, 2011', *Journal of the American Dental Association (1939),* 144(8), pp. 930-938.

Wiium, N. and Aaro, L.E. (2011) 'Outcome expectations and use of smokeless tobacco (snus): A cross-sectional study among young Norwegian snus users', *Scandinavian Journal of Psychology,* 52(1), pp. 64-70. doi: 10.1111/j.1467-9450.2010.00823.x.

Wilkinson, A.V., Koehly, L.M., Vandewater, E.A., Yu, R.K., Fisher-Hoch, S.P., Prokhorov, A.V., Kohl, H.W., Spitz, M.R. and Shete, S. (2015) 'Demographic, psychosocial, and genetic risk associated with smokeless tobacco use among Mexican heritage youth', *BMC medical genetics,* 16(1), pp. 43. doi: 10.1186/s12881-015-0188-8.

Williams Jr, R.D., Housman, J.M., Evans, J.L., Bishop, J.M., Bishop, J.M. and Ray, V. (2018) 'Urban and Rural Adolescents’ Points-of-Access for Alcohol and Tobacco', *Journal of Community Health*, 43(2), pp. 406-411. doi: 10.1007/s10900-017-0438-0.

Winn, D., Lee, Y., Hashibe, M. and Boffetta, P. (2015) 'The INHANCE consortium: toward a better understanding of the causes and mechanisms of head and neck cancer', *Oral Diseases,* 21(6), pp. 685-693. doi: 10.1111/odi.12342.

Winn, D.M. (2001) 'Tobacco use and oral disease', *Journal of dental education,* 65(4), pp. 306-312.

Woodward, M. (2014) *Epidemiology.* 3. ed. edn. Boca Raton [u.a.]: Chapman & Hall/CRC.

Wright, K., Brodie, C. and Perar, G. (2013) *Report on Paan and Smokeless Tobacco Product Use amongst Bangladeshi Women Church Street, Westminster January-May 2013.* Available at: http://www.communitychampionsuk.org (Accessed: July 18, 2018)

Wu, F., Parvez, F., Islam, T., Ahmed, A., Rakibuz-Zaman, M., Hasan, R., Argos, M., Levy, D., Sarwar, G., Ahsan, H. and Chen, Y. (2015) 'Betel quid use and mortality in Bangladesh: a cohort study’, *World Health Organisation. Bulletin of the World Health Organisation,* 93(10), pp. 684.

Wu, Y., Yen, C., Hsiao, J., Ou, C., Huang, J., Wong, T., Tsai, S., Huang, C., Lee, W., Chen, K., Fang, S., Wu, J., Hsueh, W., Lin, F., Yang, M., Chang, J., Liao, H., Wu, S., Lin, C., Wang, Y., Weng, Y., Yang, H., Chen, Y. and Chang, J.S. (2016) 'A Comprehensive Analysis on the Association between Tobacco-Free Betel Quid and

Risk of Head and Neck Cancer in Taiwanese Men', *PloS one,* 11(10), pp. e0164937. doi: 10.1371/journal.pone.0164937.

Wyss, A.B., Hashibe, M., Lee, Y.A., Chuang, S., Muscat, J., Chen, C., Schwartz, S.M., Smith, E., Zhang, Z., Morgenstern, H., Wei, Q., Li, G., Kelsey, K.T., McClean, M., Winn, D.M., Schantz, S., Yu, G., Gillison, M.L., Zevallos, J.P., Boffetta, P. and Olshan, A.F. (2016) 'Smokeless Tobacco Use and the Risk of Head and Neck Cancer: Pooled Analysis of US Studies in the INHANCE Consortium', *American Journal of Epidemiology,* 184(10), pp. 703-716. doi: 10.1093/aje/kww075.

Xue, J., Yang, S. and Seng, S. (2014) 'Mechanisms of Cancer Induction by Tobacco-Specific NNK and NNN', *Cancers,* 6(2), pp. 1138-1156. doi: 10.3390/cancers6021138.

Yarbrough, S.S. and Braden, C.J. (2001) 'Utility of health belief model as a guide for explaining or predicting breast cancer screening behaviours', *Journal of Advanced Nursing,* 33(5), pp. 677-688. doi: 10.1046/j.1365-2648.2001.01699.x.

Yuan, Y. and Hunt, R.H. (2009) 'Systematic Reviews: The Good, the Bad and the Ugly', The American journal of gastroenterology, 104(5), pp. 1086-1092. doi: 10.1038/ajg.2009.118.

Zaman, M., Bhuiyan, M., Fernando, T., Huq, S., Rahman, M. and Sinha, D. (2014) 'Dual use of tobacco among Bangladeshi men', *Indian Journal of Cancer,* 51(5), pp. 46. doi: 10.4103/0019-509X.147481.

Zaman, M.M., Ahmed, J., Choudhury, S.R., Ahmed, M. and Zissan, T. (2016b) 'Hypertension Clinic Service is a Good Opportunity for Tobacco Cessation in Bangladeshi Villagers', *Cardiovascular Journal,* 9(1), pp. 19. doi: 10.3329/cardio.v9i1.29535.

Zaman, M.M., Rahman, M.M., Rahman, M.R., Bhuiyan, M.R., Karim, M.N. and Chowdhury, M.A.J. (2016a) 'Prevalence of risk factors for non-communicable diseases in Bangladesh: Results from STEPS survey 2010', *Indian journal of public health,* 60(1), pp. 17-25. doi: 10.4103/0019-557X.177290.

Zavras, A.I., Douglass, C.W., Joshipura, K., Wu, T., Laskaris, G., Petridou, E., Dokianakis, G., Segas, J., Lefantzis, D., Nomikos, P., Wang, Y.F. and Diehl, S.R. (2001) 'Smoking and alcohol in the etiology of oral cancer: gender-specific risk profiles in the south of Greece', *Oral Oncology,* 37(1), pp. 28-35. doi: 10.1016/S1368-8375(00)00060-9.

Zeng, X., Leng, W., Zhang, C., Liu, J., Cao, S. and Huang, W. (2015) 'Meta-analysis on the association between toothbrushing and head and neck cancer', *Oral Oncology,* 51(5), pp. 446-451. doi: 10.1016/j.oraloncology.2015.02.095.

Zhou, J., Michaud, D.S., Langevin, S.M., McClean, M.D., Eliot, M. and Kelsey, K.T. (2013) 'Smokeless tobacco and risk of head and neck cancer: Evidence from a case–control study in New England', *International Journal of Cancer,* 132(8), pp. 1911-1917. doi: 10.1002/ijc.27839.

Znaor, A., Brennan, P., Gajalakshmi, V., Mathew, A., Shanta, V., Varghese, C. and Boffetta, P. (2003) 'Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men', *International Journal of Cancer,* 105(5), pp. 681-686. doi: 10.1002/ijc.11114.

Appendix A- Published article and conference abstract

PeerJ

Smokeless tobacco use: pattern of use, knowledge and perceptions among rural Bangladeshi adolescents

Md Zahid Ullah[1], Jennifer NW Lim[2], Marie-Ann Ha[1] and Md Mostafizur Rahman[3]

[1] Faculty of Medical Science, Anglia Ruskin University, Cambridge, United Kingdom
[2] Faculty of Education, Work and Health, University of Wolverhampton, Wolverhampton, United Kingdom
[3] Department of Oral Surgery, Dhaka Dental College and Hospital, Dhaka, Bangladesh

ABSTRACT

Background. The aim of the study was to investigate the practice and pattern of smokeless tobacco (SLT) use as well as the knowledge and perception about its ill effects among rural Bangladeshi adolescents.

Methods. A cross-sectional survey was conducted among students aged 13–18 years in two rural secondary schools in Bangladesh in August 2015. Data were collected through a self-administered questionnaire which consists of topics derived from the Social Cognitive Theory and Health Belief Model (personal characteristics, environmental factors, self-efficacy, outcome expectancies, perceived susceptibility, perceived severity, perceived benefits, perceived barriers, and cues to action). Data analysis was performed using SPSS version 24. A descriptive analysis was conducted to determine the current pattern of SLT use and knowledge about its ill effects. A chi-square test and Fisher exact test were conducted to explore associations between variables. Lastly, a logistic regression model was used to locate the predictors for current SLT use.

Results. A total of 790 students participated in the study. Among them, 9.5% (75) had used SLT at least once and 3.7% (29) were current SLT users. Males had a higher incidence of SLT use compared with females. The majority of students (77.3%) initiated SLT use between 10–13 years of age. 'Zarda' was the most common type of SLT used and most of the current users (86%) were able to buy SLT without age restrictions. Most of the current users (90%) wanted to quit SLT immediately; however, professional help was not available in schools. Overall, students had a good knowledge about the harmful effects of SLT with 54.8% (428) of respondents scoring in the good knowledge category. However, the majority of never SLT users (55.4%; 396) had a good knowledge compared to ever SLT users (42.7%; 32). Significant predictors of current SLT use included being a student aged 14 years and above (OR = 6.58, 95% CI [2.23–28.31]) as well as the variables of self-efficacy (OR = 5.78, 95% CI [1.46–19.65]), perceived barriers (OR = 0.30, 95% CI [0.10–0.74]), perceived benefit (OR = 0.21, 95% CI [0.05–1.03]) and perceived severity (OR = 0.36, 95% CI [0.16–0.91]).

Discussion. This study demonstrates the need for comprehensive prevention and control programme in rural schools targeting young adolescents. Effective measure should be taken to reshape the attitude of rural adolescents towards self-confidence and competence, as to prevent SLT use.

Submitted 23 February 2018
Accepted 26 July 2018
Published 21 August 2018

Corresponding authors
Md Zahid Ullah,
mohammad.ullah@pgr.anglia.ac.uk
Jennifer NW Lim,
JenniferNW.lim@wlv.ac.uk

Academic editor
Charlie Zhang

Additional Information and Declarations can be found on page 13

DOI 10.7717/peerj.5463

How to cite this article Ullah et al. (2018), Smokeless tobacco use: pattern of use, knowledge and perceptions among rural Bangladeshi adolescents . PeerJ 6:e5463; DOI 10.7717/peerj.5463

Subjects Epidemiology, Public Health
Keywords Smokeless tobacco, Adolescents, Rural Bangladesh, Health belief model, Social cognitive theory

INTRODUCTION

Globally, more than 300 million people are currently using smokeless tobacco (SLT). Moreover, at least one in 10 adolescents aged 13 to 15 years use tobacco and this figure is much higher in low-income countries. A recent review of studies from 113 countries revealed that SLT use alone accounts for loss of over 6 million disability-adjusted-life-years (DALYs) and has caused 266,592 deaths from cancers and heart disease. Almost 85% of the global disease burden of SLT use is from the South Asia region, of which India accounts for 74% and Bangladesh accounts for 5% (*Siddiqi et al., 2015*).

SLT is used in a wide variety of forms in many countries of the world. Specifically, SLT is used orally by chewing, sucking, sniffing or applying it to the teeth or gums (toothpaste or powder) or inserting it in betel quid (*National Cancer Institute and Centers for Disease Control and Prevention, 2014*; *IARC, 2007*). The most popular forms of SLT products in South Asia are Zarda, Pan Masala, Khaini and Gul (*Mutti et al., 2016*). SLT products contain roughly 4,000 types of chemicals, including nicotine, carcinogens and other toxic chemicals, which are believed to cause negative health effects (*Khariwala et al., 2013*; *Perfetti & Rodgman, 2012*). Based on evidence from available epidemiological studies, the International Agency for Research on Cancer (IARC) concluded that SLT products, such as chewing tobacco, snuff or betel quid, are carcinogenic to humans (*IARC, 2007*).

Adolescents are at a stage of their life where they face different attractive choices of habits and these choices may change their future lifestyle (*Ernst, Pine & Hardin, 2006*). Using tobacco at an early age may lead to tobacco dependency, creating a strong addiction in early life and a difficult habit to quit (*Kaduri et al., 2008*). According to the WHO, three out of five adolescents who try any type of tobacco are more likely to become regular smokers in adulthood and consider other substance use (*WHO, 1998*). Regarding the long-term adverse effects of SLT use, adolescents are predisposed to a higher risk of oral cancer, oral mucosal lesions, periodontal diseases and heart disease in their middle age, which is also the most productive age of one's life (*National Cancer Institute and Centers for Disease Control and Prevention, 2014*).

Several behavioural theories have been used to explain SLT initiation, continuation and cessation among adolescents, with social cognitive theory (SCT) and the health belief model (HBM) being the most widely used (*Creamer et al., 2018*; *Cavazos-Rehg et al., 2016*; *Mantler, 2013*; *Nemeth et al., 2012*). The SCT is one of the components of behaviourism, as it explains why an individual acquires and maintains certain behavioural patterns, such as SLT use (*Bandura, 1986*). In contrast, the HBM is a psychological model that attempts to explain and predict adolescents' health behaviours by focusing on the attitudes and beliefs of an individual (*Glanz, Rimer & Viswanath, 2015*). Identification of social cognitive and HBM predictors of adolescent SLT use would be a primary step towards explaining this behaviour and for planning and developing SLT cessation interventions.

In Bangladesh, 57,000 people die and 1.2 million people suffer from tobacco-related diseases every year. More than 4.3 million people use different forms of tobacco and the health cost of tobacco-related diseases are double that of the revenue generated from this sector (*WHO, 2015*). SLT use contributed to a total of 320,000 DALYs lost and 13,329 deaths due to cancers and heart disease in Bangladesh alone (*Siddiqi et al., 2015*). Bangladeshi adolescents are facing a double challenge from smoking and SLT use, as SLT use is as prevalent as smoking tobacco in Bangladesh (*National Cancer Institute and Centers for Disease Control and Prevention, 2014*). Overall, 6.9% of Bangladeshi adolescents use any form of tobacco, but the exact number of adolescent SLT users is unknown (*National Cancer Institute and Centers for Disease Control and Prevention, 2014*; *WHO, 2009*). The recent Global Youth Tobacco Survey (GYTS) in Bangladesh reported that current SLT prevalence among school students aged 13 to 15 years was 4.5% and more prevalent among boys (5.9%) compared with girls (2.0%) (*WHO, 2015*).

The availability, affordability across regions and acceptance of tobacco in some cultures play vital roles in adolescent or youth tobacco use (*Warren et al., 2009*). The use of SLT products in rural areas has been deep-rooted in the Bangladeshi culture of hospitality (*Mia et al., 2017*). In Bangladesh, using SLT is regarded as a shared social activity that is performed with friends, relatives and family members and has even been integrated into social gatherings, such as festivals, weddings and religious gatherings (*Sansone, 2014*). In Bangladeshi society, younger people hesitate to smoke before their elders and they will never use or smoke cigarettes in front of their parents or seniors. However, SLT is an exception since chewing pan or betel leaf along with tobacco products is regarded as normal social behaviour and a symbol of hospitality in the rural areas of Bangladesh (*Islam & AlKhateeb, 1995*). Moreover, SLT use in Bangladesh is more prevalent among low socio-economic and socially disadvantaged populations (*Mia et al., 2017*; *Huque et al., 2017*; *Azam et al., 2016*). The high prevalence of SLT use in Bangladesh is associated with easy availability, low price and affordability, misconceptions regarding its useful health effects, lack of tobacco control regulations and weak enforcement of existing regulations (*Huque et al., 2017*).

The purpose of the study was to examine the current pattern and practice of SLT use among adolescents in a rural part of Bangladesh and their knowledge and perception about its ill effects. Possible predictors of current SLT habits were also explored to inform health promotion and preventive measures that could be targeted at this age group.

MATERIALS AND METHODS

This was a school-based cross-sectional study conducted in two rural secondary schools in Ramgati Upazila during October 2015. Ramgati Upazila is a subdivision of the Lakshmipur district in Bangladesh with a population of 261,002 with low socio-economic status (*Bangladesh Bureau of Statistics, 2013*). It is considered a rural community due to the dominant economic activity being farming. Secondary education in this rural area of Bangladesh is provided by 18 non-governmental schools serving approximately 8,994 students (*Bangladesh Bureau of Statistics, 2013*). The literacy rate in this area (39.3%) is lower than the national average (61.5%) (*Bangladesh Bureau of Statistics, 2013*).

Ethical approval for the present study was obtained from the Anglia Ruskin University Ethics committee (Ref: NS/jc/FMSFREP/15-039) and the head teachers of the participating schools in Ramgati Upazila. Informed consent was obtained from the students' parents. Prior to the administration of the survey, the researcher (MZU) explained the study and the students were required to provide verbal consent to indicate voluntary participation. Students were informed of their right to decline participation or withdraw from the study at any time without consequence.

Sample size and sampling technique

To reach a 95% confidence level with 2.5% marginal error and 10.1% expected ever SLT prevalence, a sample size of 553 was required (*Daniel, 2009*; *WHO, 2015*). Of the 18 secondary schools in Ramgati Upazila, with a total population of 8,994 students, 790 (8.78%) were recruited from two schools using a stratified method according to the enrolment size in each school. Initially the number of students for all 18 schools was collected from the local administrative office. From there, five schools with highest enrolment size were selected and from those five schools two schools were chosen randomly from their registration number.

Survey tool and data collection

A self-administered questionnaire was adapted from the SLT module of the GYTS questionnaire version 1.00 (2012) (*Global Youth Tobacco Survey Collaborative Group, 2012*). Guided by the Social Cognitive Theory and Health Belief Model, the questionnaire was developed and comprised of closed-ended, open-ended and multiple response questions. Additional questions on types of SLT use, the reason for failing to quit SLT and eight knowledge questions were added from selected literature and validated surveys (*Bhaskar et al., 2016*; *Abdullah et al., 2014*; *Kaduri et al., 2008*).

The questionnaire was translated from English to Bengali and then back-translated to English by professional translators. It was also reviewed by the research team, local healthcare workers who had previously conducted a survey with students and teachers to ensure that the Bengali version was idiomatically appropriate for Bangladeshi adolescents. The questionnaire was piloted among five female and five male students from two secondary schools and was modified accordingly. Students took up to 15 min to complete the questionnaire.

Study measures

The dependent measure or outcome variable for the present study was SLT use, which was classified into three main categories: 'ever users', 'current users' and 'never users' (*WHO, 2015*). Ever users were individuals who had used SLT at least once in their life, even if this was a tiny portion. Current SLT users were those who used SLT at least once in the last 30 days (*WHO, 2015*). Never users had never used SLT before. Additionally, respondents were asked, "What type or brand of SLT have you tried?"

Social cognitive factors

"*Personal characteristics*" of the participants were measured by asking questions related to age, gender, father's and mother's profession, the age of initiation and SLT dependency.

"*Environmental factors*" were assessed through querying about the source and access to SLT products. "*Self-efficacy*" was measured through respondent's ability to deny SLT when offered by their friends. "*Outcome expectancies*" was measured by querying the reasons for SLT use.

Health belief model

"*Perceived susceptibility*" was measured through students' knowledge about harmful effects of SLT use and its contents, such as the development of white patches in the mouth, oral cancer, gum diseases and heart disease from SLT use. "*Perceived severity*" was assessed through asking respondents' perception about the harmfulness of SLT compared to smoked tobacco. "*Perceived benefit*" was assessed by querying about the potential benefits of SLT use. "*Perceived barriers*" was measured by asking about the difficulty of quitting SLT. "*Cues to action*" was assessed by questioning about their experience receiving help to quit SLT and noticing the health warning on SLT packages.

Data analysis

All the data were entered into MS Excel 2013 and exported into SPSS version 24 for analysis. Data analyses were conducted in multiple phases. In the first phase, a simple descriptive analysis (frequency, percentage, mean and median) was conducted to examine current SLT use behaviour as well as perception and knowledge about its ill effects. In the second phase, statistical analyses were performed to explore the association between different variables, such as socio-demographic variables, SLT use behaviours, perception and knowledge. Associations between categorical variables were assessed using a chi-square or Fisher exact test where appropriate. Knowledge was assessed using a scoring system where participants were given one point for each correctly answered question and zero otherwise. The sum of scores was calculated, and its relation to other variables was assessed using the student t-test or Mann–Whitney test when appropriate. The knowledge score was further categorised into poor knowledge (score of 0–2), average knowledge (score of 3–5), and good knowledge (score of 6–8). For the predictive model, the knowledge score was considered a nominal variable.

In the third phase, a multivariate logistic regression model was used to predict current SLT use. However, initially a univariate logistic regression was performed to determine variables that could be used to predict current SLT use. Akaike information criterion (AIC) was also extracted for each variable. Some variables were presented with different cut-off values. Each of them was assessed, and the variable with the lowest AIC was included in the final model. Only variables that were significant in the initial screening (univariate logistic regression) were included in the multivariate logistic regression. A correlation matrix was also constructed to ensure the absence of multicollinearity between variables included in the model. Exponentiated coefficients (odds ratio) were extracted from the model as well as the overall AIC of the model. Confidence intervals (95%) and Wald statistics were used to assess whether regression coefficients were significantly different from zero (null hypothesis). A receiver operator characteristics curve was plotted to assess whether the model could accurately classify the data. The Area Under the Curve (AUC) was 0.84 which is a good indicator of the model's predictive power.

Table 1 Socio-demographic characteristics of the study participants.

Characteristics	Categories	Total % (*n*)	Ever SLT users	Non-users
Gender	Male	63.3% (500)	68.0% (51)	62.8% (449)
	Female	36.7% (290)	32.0% (24)	37.2% (266)
Age	13 or younger	40.4% (319)	16.0% (12)	42.9% (307)
	14	29.0% (229)	34.7% (26)	28.4% (203)
	15 or older	30.6% (242)	49.3% (37)	28.8% (205)
Father's job	Farming	62.4% (493)	62.7% (47)	62.4% (446)
	Business	18.4% (145)	18.7% (14)	18.3% (131)
	Gov. employee	1.4% (11)	8.0% (6)	0.7% (5)
	Non-Gov. employee	6.1% (48)	4.0% (3)	6.3% (45)
	Doctor	1.3% (10)	1.3% (1)	1.3% (9)
	Teacher	3.0% (24)	2.7% (2)	3.1% (22)
	Daily labourer	1.9% (15)	0%	2.1% (15)
	Unemployed	0.4% (3)	1.3% (1)	0.3% (2)
	Others	5.2% (41)	1.3% (1)	5.6% (40)
Mother's job	Housework	98.9% (781)	98.7% (74)	98.9% (707)
	Gov. employee	0.3% (2)	0%	0.3% (2)
	Teacher	0.9% (7)	1.3% (1)	0.8% (6)

Notes.
Others: Did not mention father's profession.
SLT, Smokeless tobacco.

The odds ratio with a 95% CI was used to quantify the association. For the purpose of the analysis, a *P*-value of less than 0.05 was considered significant. Continuous variables were expressed as means or medians, whereas categorical variables were presented in frequencies or percentages. Data were missing for some of the questions; therefore, percentages were expressed according to the number of valid responses.

RESULTS

Sample characteristics

Of the 820 enrolled students, 790 attended school on the day of the survey and all the students gave consent and participated in the study. More than half of the participants were male (63.3%). The mean age was 13.8 ± 0.07 years, and the median age was 14 years. There was no significant difference in the mean age of male (14.0 ± 0.07) and female students (13.7 ± 0.07). The predominant occupation of the participants' fathers was farming (62.4%; 493), and almost all the participants' mothers were housekeepers (98.9%; 781) (Table 1).

SLT use behaviour

A total of 9.5% (75) reported ever using SLT. Approximately 3.7% (29) of the participants in this study or 38.7% of the ever users reported that they were currently using SLT. Males had a higher incidence of both ever and current SLT use with 68% (51) and 65.5% (19), respectively. Among the ever users, participants reported they started SLT use as early as the age of 7 years or younger (5.3%; four). However, most SLT users reported using SLT at the age of 12 or 13 years (34.7%; 25). Male SLT users (35.3%; 18) started using SLT at an earlier age (10–11 years) compared to female users (12–13 years) (41.7%; 10) (Table 2). Only two types of SLT were popular among the SLT users. Zarda was the most common type of SLT used (80%) followed by Pan Masala (20%) (Table 2). The majority used SLT less than once per day (65.5%; 19). Overall SLT dependency was low, where 89.3% (67) and 84% (63) of SLT users did not feel the need to use SLT first thing in the morning and did not feel a strong desire to use it again after using it once, respectively. Many respondents could not articulate their reason for using SLT (36.7%; 29). However, only male users (9.3%; five) and respondents aged 14 years and above (7.9%; five) used SLT because their friends also used. Regarding SLT cessation, 89.7% (26) of current SLT users wanted to quit, but none of them received help or advice from a program or professionals to do so. Regarding the attempt to quit SLT in the past 12 months, 34.5% (10) of current SLT users tried to stop SLT but failed. Between both genders, male students (42.1%; eight) had a higher rate of failure in quitting SLT compared with female students (20.0%; two) (Table 2).

Regarding access and availability, many students obtained SLT from social sources (41.4%; 12) and from stores and shops (34.4%; 10). Among current users who bought SLT products, 86% (12) were not refused because of their age. In terms of their exposure to the anti-tobacco messages, 45.3% (34) of respondents reported not seeing any health warning on SLT packages. In contrast, 29.3% (22) students had seen the health warnings and thought of quitting SLT.

The overall susceptibility to SLT use was 2.8% (22) when offered by friends and was significantly associated with ever SLT use. Specifically, 8% (six) of ever SLT users compared to 2.2% (16) of never users were likely to use SLT if offered by their friend ($p = 0.01$). The majority of students (59%; 466) thought it would not be difficult to quit once someone started using SLT and this was significantly associated with age. Specifically, 52.9% (128) of respondents 15 years or older believed it would be difficult to quit SLT compared to 35.8% (196) of respondents less than 15 years old ($p < 0.001$).

Knowledge about the harmful effects of SLT

To assess respondents' knowledge about the adverse effects of SLT, students were asked eight questions. The overall knowledge about the harmful effects of smokeless tobacco use was good among respondents. The majority of adolescents (75.6%; 597) thought SLT use is bad for health. However, 21.2% (169) of study participants did not know whether SLT use is bad or good for the health. Over 32% (254) of students did not know whether SLT is less harmful compared to smoked tobacco (ST) and 25% (202) thought it is less harmful than ST. Additionally, 29.2% (231), 25.3% (200), 26% (206), and 25.4% (201) of students did not know SLT causes white patches in the mouth, oral cancer, gum diseases, and heart diseases respectively. Also, 32.5% (257) of respondents did not know SLT contains Nicotine.

The mean knowledge score was 5.19 ± 0.15. Male students (5.36 ± 0.09) were more likely to be knowledgeable compared to female students (4.9 ± 0.12). Students whose fathers' profession was teaching (6.21 ± 0.37) had the highest mean score, and the lowest score was seen from students whose fathers' occupation was farming (5.08 ± 0.09). Moreover, the average knowledge score was lowest among current SLT users (4.31 ± 0.40) followed

Table 2 Distribution of various factors across gender.

Measures	Categories	Male (n)	Female (n)	Total (n)	P-value
Ever SLT use	Never	62.8% (449)	37.2% (266)	100% (715)	0.38[a]
	Ever	68.0% (51)	32.0% (24)	100% (75)	
Current SLT use	No	63.2% (481)	36.8% (280)	100% (761)	0.84[a]
	Yes	65.5% (19)	34.5% (10)	100% (29)	
SLT type	Zarda	76.5% (39)	87.5% (21)	80.0% (60)	0.36[a]
	Panmasala	23.5% (12)	12.5% (3)	20.0% (15)	
Age of initiation	≤ 7	7.8% (4)	0.0%	5.3% (4)	**0.03**[b]
	8–9 years	3.9% (2)	8.3% (2)	5.3% (4)	
	10–11 years	35.3% (18)	25.0% (6)	32.0% (24)	
	12–13 years	31.4% (16)	41.7% (10)	34.7% (26)	
	14–15 years	21.6% (11)	25.0% (6)	22.7% (17)	
Number of days used	Did not use	62.7% (32)	58.3% (14)	61.3% (46)	0.28[b]
	1 to 2 days	27.5% (14)	16.7% (4)	24.0% (18)	
	3 to 5 days	5.9% (3)	20.8% (5)	10.7% (8)	
	20 to 29 days	0.0%	4.2% (1)	1.3% (1)	
	All 30 days	3.9% (2)	0.0%	2.7% (2)	
Frequency per day (current)	Less than once per day	63.2% (12)	70.0%(7)	65.5% (19)	0.71[a]
	At least Once per day	36.8% (7)	30.0% (3)	34.5% (10)	
Use SLT, first thing in the morning	No	90.2 % (46)	87.5%(21)	89.3%(67)	0.78[b]
	Yes sometimes	7.8% (4)	12.5% (3)	9.3% (7)	
	Yes always	2.0% (1)	0.0%	1.3% (1)	
Desire to use SLT again	Never	80.4% (41)	91.7% (22)	84.0% (63)	0.88[b]
	Within 60 minutes	9.8% (5)	8.3% (2)	9.3% (7)	
	1 to 2 hours	5.9% (3)	0.0%	4.0% (3)	
	1 to 3 days	2.0% (1)	0.0%	1.3% (1)	
	4 days or more	2.0% (1)	0.0%	1.3% (1)	
Reasons of using	Taste	13.0% (7)	12.0% (3)	12.7% (10)	0.47[b]
	Smell	5.6% (3)	4.0% (1)	5.1% (4)	
	Pleasure	27.8% (15)	28.0% (7)	26.7% (20)	
	Feels better	0.0%	4.0% (1)	1.3% (1)	
	Friend does	9.3% (5)	0.0%	6.3% (5)	
	Don't know	37.0% (20)	36.0% (9)	36.7% (29)	
	Other reason	7.4% (4)	16.0% (4)	10.1% (8)	
Want to stop (Current)	Yes	94.7% (18)	80.0% (8)	89.7% (26)	0.58[b]
	No	5.3% (1)	20.0% (2)	10.3% (3)	
Tried to stop (Current)	Tried but unsuccessful	42.1% (8)	20.0% (2)	34.5% (10)	0.13[a]
	Did not try to quit	57.9% (11)	80.0% (8)	65.5% (19)	
Source of help to quit (Current)	A Program	0.0%	0.0%	0.0%	0.54[b]
	Friend	42.1% (8)	0.0%	27.6% (8)	
	Family	31.6% (6)	80% (8)	43.8% (14)	
	No help	26.3% (5)	20.0% (2)	24.1% (7)	

(*continued on next page*)

Table 2 (*continued*)

Measures	Categories	Male (*n*)	Female (*n*)	Total (*n*)	*P*-value
Source of SLT	School Shop	4.8% (1)	12.5% (1)	6.9% (2)	0.52[a]
	Street Vendor	14.3% (3)	0.0%	10.3% (3)	
	Someone else	38.1% (8)	50.0% (4)	41.4% (12)	
	Store near house	19.0% (4)	0.0%	13.8% (4)	
	Got it other way	23.8% (5)	25.0% (2)	24.1% (7)	
	On the way to school	0.0%	12.5% (1)	3.4% (1)	
Refuse to sell SLT	No	62.5% (10)	71.4% (5)	65.2% (15)	0.68[a]
	Yes	37.5% (6)	28.6% (2)	34.8% (8)	
Health Warnings	No	47.1% (24)	41.7% (10)	45.3% (34)	0.80[a]
	Yes, didn't care	17.6% (9)	41.7% (10)	25.3% (19)	
	Yes, thought of quitting	35.3% (18)	16.7% (4)	29.3% (22)	
If offered by a Friend	No	97.8% (489)	96.2% (279)	97.2% (768)	0.26[a]
	Yes	2.2% (11)	3.8% (11)	2.8% (22)	
Difficult to quit	No	60.0% (300)	57.2% (166)	59.0% (466)	0.45[a]
	Yes	40.0% (200)	42.8% (124)	41.0% (324)	

Notes.
SLT, Smokeless Tobacco.
[a]Chi-Square Test.
[b]Fisher-Exact test
Significant results are bold.

by ever users (4.48 ± 0.20), and the highest average score was from the group who never tried SLT (5.27 ± 0.08).

Table 3 represents the knowledge category across various factors. Respondents were grouped into three main categories based on the total score distribution (poor knowledge, average knowledge, good knowledge). Overall, 54.2% (428) of respondents had good knowledge about the harmful effects of SLT. The majority of never SLT users (55.4%; 396) scored in the good knowledge category compared to ever users (42.7%; 32). Male respondents were more familiar with the SLT use hazards (56%) compared to females (51%) (Table 3). Knowledge was significantly associated with witnessing anti-tobacco messages on the SLT packages. Specifically, 61.8% (21) of ever SLT users who did not witness anti-tobacco messages on SLT packages had good knowledge compared to 26.8% who did see the anti-tobacco messages ($\chi 2 = 9.87$, $p = 0.007$, $\varphi = 0.363$). Knowledge was also significantly associated with respondent's self-efficacy, where 55.2% (424) of respondents who would refuse to use SLT if offered by a friend had good knowledge compared to 18.2% (four) of those who would use SLT ($\chi 2 = 11.98$, $p = 0.003$, $\varphi = 0.123$). In addition, perceived barriers were significantly associated with knowledge, as 21.9% (102) of respondents who thought it would not be difficult to quit SLT once started had poor knowledge compared to 9.6% (31) of those who thought the opposite ($\chi 2 = 20.95$, $p =< 0.001$, $\varphi = 0.163$) (Table 3).

Predictors of current SLT use

Initial univariate logistic regression analysis showed that age ($p = 0.005$), father's profession ($p = 0.046$), self-efficacy ($p = 0.001$), perceived barriers ($p = 0.029$), perceived benefit

Table 3 Distribution of knowledge index across various factors.

Measures	Category	Poor knowledge	Average knowledge	Good knowledge	*P*-value
Smokeless tobacco use status	Never users	15.9% (114)	28.7% (205)	55.4% (396)	0.05[a]
	Ever users	25.3% (19)	32.0% (24)	42.7% (32)	
	Current use	27.6% (8)	24.1% (7)	48.3% (14)	0.28[a]
Gender	Male	14.6% (73)	29.4% (147)	56.0% (280)	0.08[a]
	Female	20.7% (60)	28.3% (82)	51.0% (148)	
Age	14 < years	18.5% (59)	26.3% (84)	55.2% (176)	0.32[a]
	≥ 14 years	15.7% (74)	30.8% (145)	53.5% (252)	
Father's profession	Farmer	18.2% (93)	29.5% (151)	52.3% (267)	0.25[a]
	Other	14.3% (40)	28.0% (78)	57.7% (161)	
Age of initiation	≤ 7 years	25.0% (1)	0.0%	75.0% (3)	0.17[a,b]
	8–9	0.0%	0.0%	100.0% (4)	
	10–11	20.8% (5)	33.3% (8)	45.8% (11)	
	12–13	23.1% (6)	46.2% (12)	30.8% (8)	
	14–15	41.2% (7)	23.5% (4)	35.3% (6)	
Want to quit	Yes	30.2% (13)	34.9% (15)	34.9% (15)	0.54[a]
	No	12.5% (1)	37.5% (3)	50.0% (4)	
Tried to quit last year	Yes	9.5% (2)	38.1% (8)	52.4% (11)	0.49[a]
	No	22.2% (12)	29.6% (16)	48.1% (26)	
Health warning	Yes	29.3% (12)	43.9% (18)	26.8% (11)	**0.007**[a]
	No	20.6% (7)	17.6% (6)	61.8% (21)	
If offered by friend	Yes	27.3% (6)	54.5% (12)	18.2% (4)	**0.003**[a]
	No	16.5% (127)	28.3% (217)	55.2% (424)	
Difficult to quit	Yes	9.6% (31)	32.4% (105)	58.0% (188)	**<0.001**[a]
	No	21.9% (102)	26.6% (124)	51.5% (240)	

Notes.
[a]Chi-Square Test.
[b]Fisher-Exact test.
Significant results are bold.

($p = 0.014$) and perceived severity ($p = 0.008$) were significant variables (Table 4). In the next stage, these variables were included in the multivariate logistic regression.

The multivariate regression analysis indicated that students who were 14 years old and older were 6.5 times more likely to be current SLT users compared to those younger than 14 years ($p = 0.002$) (Table 4). Perceived benefits and perceived severity of SLT use was associated with lower odds of current SLT use (OR = 0.21, 95% CI [0.059–1.03] and OR = 0.36, 95% CI [0.12–0.97], respectively) (Table 5). Self-efficacy was also a significant predictor of current SLT use where students who would use SLT if offered by a friend were more likely to be current SLT users compared to those who would not (OR = 5.78, 95% CI [1.46–19.65]). Lastly, perceived barriers regarding the difficulty of quitting SLT use was also a significant predictor of current SLT use where those who perceived quitting as easy were more likely to be current users compared to those who did not (OR = 0.30, 95% CI [0.10–0.74]) (Table 5). The model correctly classified 82% of the dependent variables.

Table 4 Univariate regression analysis.

Labels	*P*-value	Odds ratio	AIC
Gender	0.800	0.904	252.532
Age (≥14 years)	**0.003**	6.154	239.14
Father's profession	0.153	0.413	257.132
Farmer vs other (Other)	**0.046**	0.37	247.781
Mother's profession	0.994	0	253.92
If someone offered you SLT, would you use it? (Yes)	**0.001**	6.604	245.285
Is it difficult to quit? (Yes)	**0.029**	0.363	247.001
Do you think SLT use is good for health?	0.106	6.875	252.882
Are there benefits of SLT to your body and health?	**0.014**	0.198	248.212
Does SLT cause less harm to your health compared to smoking tobacco?	**0.008**	0.268	243.674
Does SLT cause white patches in the mouth?	0.253	0.649	251.294
Can SLT cause oral cancer?	0.342	1.494	251.646
Does SLT cause gum diseases?	0.658	0.843	252.403
Does SLT cause heart diseases?	0.260	0.652	251.341
Does SLT contain nicotine?	0.079	0.509	249.454

Notes.
SLT, Smokeless tobacco.
Reference Group: Never used SLT, *AIC Akaike information criterion*.
Significant results are bold.

Table 5 Multivariate analysis result.

Variables	Odds Ratio	SE	Wald statistic	*P*-value	95% CI for odds ratio	
					Lower	Upper
Intercept	0.083	0.07	−2.95	**0.003**	0.01	0.36
Age (≥14 years)	6.58	4.12	3.00	**0.002**	2.23	28.31
Are there benefits of smokeless tobacco to your body and health? (Yes) (Perceived benefit)	0.21	0.15	−2.17	**0.029**	0.05	1.03
Does smokeless tobacco cause less harm to health compare to smoking tobacco? (Yes) (Perceived severity)	0.36	0.185	−1.98	**0.046**	0.16	0.91
If someone offered you SLT, would you use it? (yes) (Self-efficacy)	5.78	3.75	2.70	**0.006**	1.46	19.65
Is it difficult to quit? (yes) (Perceived barrier)	0.30	0.14	−2.44	**0.014**	0.10	0.74
Father's job (Other Job)	0.41	0.21	−1.701	0.08	0.13	1.05

Notes.
Reference Group: Never used SLT, CI, Confidence Interval; SE, Standard Error; SLT, Smokeless Tobacco.
Significant results are bold.

DISCUSSION

This is the first comprehensive study examining the current practice and pattern of SLT use and knowledge about the harmful effects among adolescents in the rural areas of Bangladesh. In our study, the current prevalence of SLT use was 3.7%, whereas existing GYTS, Bangladesh (2013) report showed that the national-level prevalence among adolescents was 4.5% (*WHO, 2015*). This declining trend could be explained by the recent implementation of the 15% Value Added Tax (VAT) and 30% supplementary duty on SLT products by the Bangladesh Government (*Nargis, Hussain & Fong, 2014*). The positive relation between the tax increase and decline of youth tobacco use was also reported in previous studies (*Levy et al., 2017*; *Huang & Chaloupka, 2012*). When compared with other South-East Asian countries, the current SLT prevalence in this study was higher than Indonesia, Sri Lanka and Thailand and Bhutan, and conversely lower than India, Nepal, Myanmar, Maldives and Timor-Thistle (*National Cancer Institute and Centers for Disease Control and Prevention, 2014*). The higher percentage of SLT use among boys in the present study showed similar trends to other South-East Asian countries: Bhutan (boys 27.2%; girls 19.8%), India (boys 11.1%; girls 6.0%) and Myanmar (boys 15.2%; girls 4.0%) (*Sinha et al., 2014*). Indeed, the cultural backdrop and symbols of maturity may play a key role in this trend (*Hussain, Zaheer & Shafique, 2017*).

The findings of the present study on early SLT initiation ties well with previous studies where adolescents started using SLT as early as 12 years old or younger (*Liu et al., 2015*; *Muttapppallymyalil, Sreedharan & Divakaran, 2010*; *Kaduri et al., 2008*). Initiating SLT at an early age may lead to tobacco dependency in the future (*Haddock et al., 2001*). This scenario stresses the need to extend the coverage of the Bangladesh anti-SLT campaign to primary school students (5th grade) rather than just focusing on secondary schools (6th grade onwards). Simultaneously, designing an effective adolescent SLT cessation campaign is challenging because adolescents have easy access to different forms of tobacco in the market as evidenced by the initiation of smoked tobacco being highest in the 12–13 years age group in the country (*Arora et al., 2010*). Therefore, a cessation programme that addresses the multiple forms of tobacco use in Bangladesh would be more effective (*Sidhu et al., 2016*). The necessity of a cessation programme was also stressed from another key finding of this study where the majority of current SLT users wanted to quit SLT but received no professional help. The lack of help from health promotion boards and health professionals was also reported by the WHO. In particular, only 8.9% students in Bangladesh had received help from a programme or professional to quit smoking (*WHO, 2015*). Much work is needed to increase the capacity to promote cessation of SLT in this population group.

Access and availability play a key role in influencing adolescent SLT use. Bangladesh has a law that bans selling SLT to and by minors (*WHO, 2013*). However, in line with the previous study, our study results showed the majority of students were able to buy SLT from stores without any restriction (*Islam et al., 2016*). Additionally, since May 2013, a new tobacco control amendment was put in place that requires graphic health warnings to be printed on tobacco (smoked / SLT) packages that cover at least 50% of the principal surface area (*WHO, 2013*). Nevertheless, our study findings demonstrated poor implementation of this law in the rural areas of Bangladesh.

Multivariate logistic regression analysis showed several constructs were strong predictors of current SLT use, namely, perceived benefit, perceived severity, self-efficacy and perceived barriers. These findings demonstrate the need for an effective anti-SLT campaign in rural areas of Bangladesh addressing the above factors to improve knowledge and perception of SLT use and its ill effects. Previous study results showed that health education campaigns based on the HBM and social cognitive factors were effective in improving knowledge and attitude about tobacco use hazards and enhancing success in quitting tobacco and preventing relapse (*Elshatarat et al., 2016*; *Renuka & Pushpanjali, 2014*).

We used a validated questionnaire from the WHO's GYTS that enabled comparison of our results with other similar studies in the field. However, our study is not without limitations. Firstly, we did not have any information related to parental SLT use. In addition, the study was conducted in a rural area of Bangladesh and our results are therefore not generalisable to urban areas. Moreover, we collected self-reported data whereby both underreporting and over-reporting by the participants were plausible. Another limitation was not including adolescents who do not go to school, as they tend to have a higher risk of using tobacco and other substances (*Kautilya, Sathish & Hegde, 2015*).

CONCLUSION

Our evidence suggests that SLT use in the rural areas of Bangladesh is low compared to other neighbouring countries. However, initiation of SLT at an early age is a public health concern. Lack of professional help to quit SLT and poor implementation of tobacco control laws were prevalent. Overall knowledge about SLT use and its ill effects was good, but this score was lower among SLT users compared to non-users. Professional help to quit SLT, tightening the tobacco control laws in rural areas and developing an educational health campaign focusing on young adolescents and different forms of tobacco use can reduce the current and future burden of adolescents SLT use in rural areas of Bangladesh.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding

The authors received no funding for this work.

Competing Interests

The authors declare there are no competing interests.

Author Contributions

- Md Zahid Ullah conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
- Jennifer NW Lim and Marie-Ann Ha conceived and designed the experiments, authored or reviewed drafts of the paper, approved the final draft.

- Md Mostafizur Rahman performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, approved the final draft.

Human Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

Ethical approval for the present study was obtained from the Anglia Ruskin University Ethics committee (Ref: NS/jc/FMSFREP/15-039).

Data Availability

The following information was supplied regarding data availability:

The raw data are provided in a Supplemental File.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.5463#supplemental-information.

REFERENCES

Abdullah AS, Driezen P, Ruthbah HU, Nargis N, Quah A, Fong TG. 2014. Patterns and predictors of smokeless tobacco use among adults in Bangladesh: findings from the International Tobacco Control (ITC) Bangladesh survey. *PLOS ONE* **9**:e101934 DOI 10.1371/journal.pone.0101934.

Arora M, Tewari A, Tripathy V, Nazar GP, Juneja NS, Ramakrishnan L, Reddy KS. 2010. Community-based model for preventing tobacco use among disadvantaged adolescents in urban slums of India. *Health Promotion International* **25**:143–152 DOI 10.1093/heapro/daq008.

Azam NM, Shahjahan M, Yeasmin M, Ahmed UN. 2016. Prevalence of smokeless tobacco among low socioeconomic populations: a cross-sectional analysis. *PLOS ONE* **11**:e0156887 DOI 10.1371/journal.pone.0156887.

Bandura A. 1986. *Social foundations of thought and action: a social cognitive theory*. 2nd edition. Englewood Cliffs: Prentice-Hall.

Bangladesh Bureau of Statistics. 2013. *District Statistics 2011 (Bangladesh)*. Lakshmipur District: Bangladesh Bureau of Statistics.

Bhaskar RK, Sah MN, Gaurav K, Bhaskar SC, Singh R, Yadav MK, Ojha S. 2016. Prevalence and correlates of tobacco use among adolescents in the schools of Kalaiya, Nepal: a cross-sectional questionnaire-based study. *Tobacco Induced Diseases* **14**:11 DOI 10.1186/s12971-016-0075-x.

Cavazos-Rehg PA, Krauss M, Sowles S, Spitznagel EL, Grucza R, Chaloupka FJ, Bierut LJ. 2016. Multiple levels of influence that impact youth tobacco use. *Tobacco Regulatory Science* **2**:106–122 DOI 10.18001/TRS.2.2.2.

Creamer MR, Delk J, Case K, Perry CL, Harrell MB. 2018. Positive outcome expectations and tobacco product use behaviors in youth. *Substance Use & Misuse* **53(8)**:1399–1402 DOI 10.1080/10826084.2017.1404104.

Daniel WW. 2009. *Biostatistics*. Hoboken: Wiley.

Elshatarat RA, Yacoub MI, Khraim FM, Saleh ZT, Afaneh TR. 2016. Self-efficacy in treating tobacco use: a review article. *Proceedings of Singapore Healthcare* **25**:243–248 DOI 10.1177/2010105816667137.

Ernst M, Pine DS, Hardin M. 2006. Triadic model of the neurobiology of motivated behaviour in adolescence. *Psychological Medicine* **36**:299–312 DOI 10.1017/S0033291705005891.

Glanz K, Rimer BK, Viswanath K. 2015. *Health behavior*. New York: Jossey Bass Ltd.

Global Youth Tobacco Survey Collaborative Group. 2012. Global Youth Tobacco Survey (GYTS): core questionnaire with optional questions. Version 1.0. *Available at https://www.datafirst.uct.ac.za/dataportal/index.php/catalog/645/download/9102*.

Haddock CK, Weg MV, DeBon M, Klesges RC, Talcott GW, Lando H, Peterson A. 2001. Evidence that smokeless tobacco use is a gateway for smoking initiation in young adult males. *Preventive Medicine* **32**:262–267 DOI 10.1006/pmed.2000.0802.

Huang J, Chaloupka FJ. 2012. *The impact of the 2009 federal tobacco excise tax increase on youth tobacco use*. Cambridge: National Bureau of Economic Research.

Huque R, Zaman MM, Huq SM, Sinha DN. 2017. Smokeless tobacco and public health in Bangladesh. *Indian Journal of Public Health* **61(Supplement)**:S18–S24 DOI 10.4103/ijph.IJPH_233_17.

Hussain A, Zaheer S, Shafique K. 2017. Individual, social and environmental determinants of smokeless tobacco and betel quid use amongst adolescents of Karachi: a school-based cross-sectional survey. *BMC Public Health* **17**:1–10 DOI 10.1186/s12889-017-4916-1.

IARC. 2007. Smokeless tobacco and some tobacco-specific N-nitrosamines. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* **89**:1–592.

Islam N, AlKhateeb M. 1995. Challenges and opportunities for tobacco control in the Islamic countries-a case-study from Bangladesh. *Eastern Mediterranean Health Journal* **1(2)**:230–223.

Islam SMS, Mainuddin AKM, Bhuiyan FA, Chowdhury KN. 2016. Prevalence of tobacco use and its contributing factors among adolescents in Bangladesh: results from a population-based study. *South Asian Journal of Cancer* **5**:186–188 DOI 10.4103/2278-330X.195339.

Kaduri P, Kitua H, Mbatia J, Kitua AY, Mbwambo J. 2008. Smokeless tobacco use among adolescents in Ilala Municipality, Tanzania. *Tanzania Journal of Health Research* **10**:28–33.

Kautilya VD, Sathish KV, Hegde SP. 2015. Study of substance abuse among street children near Bangalore Medical College, Bangalore. *Indian Journal of Forensic and Community Medicine* **2**:220–224 DOI 10.5958/2394-6776.2015.00009.0.

Khariwala SS, Carmella SG, Stepanov I, Fernandes P, Lassig AA, Yueh B, Hatsukami D, Hecht SS. 2013. Elevated levels of 1-hydroxypyrene and N′-nitrosonornicotine in smokers with head and neck cancer: a matched control study. *Head & Neck* **35**:1096–1100 DOI 10.1002/hed.23085.

Levy DT, Mays D, Boyle RG, Tam J, Chaloupka FJ. 2017. The effect of tobacco control policies on US smokeless tobacco use: a structured review. *Nicotine & Tobacco Research* **20**:3–11 DOI 10.1093/ntr/ntw291.

Liu ST, Nemeth JM, Klein EG, Ferketich AK, Kwan M, Wewers ME. 2015. Risk perceptions of smokeless tobacco among adolescent and adult users and nonusers. *Journal of Health Communication* **20**:599–606 DOI 10.1080/10810730.2015.1012237.

Mantler T. 2013. A systematic review of smoking youths' perceptions of addiction and health risks associated with smoking: utilizing the framework of the health belief model. *Addiction Research & Theory* **21**:306–317 DOI 10.3109/16066359.2012.727505.

Mia MN, Hanifi SMA, Rahman MS, Sultana A, Hoque S, Bhuiya A. 2017. Prevalence, pattern and sociodemographic differentials in smokeless tobacco consumption in Bangladesh: evidence from a population-based cross-sectional study in Chakaria. *BMJ Open* **7**:e012765 DOI 10.1136/bmjopen-2016-012765.

Muttapppallymyalil J, Sreedharan J, Divakaran B. 2010. Smokeless tobacco consumption among schoolchildren. *Indian Journal of Cancer* **47(Suppl 1)**:19–23 DOI 10.4103/0019-509X.63872.

Mutti S, Reid J, Gupta P, Pednekar M, Dhumal G, Nargis N, Hussain A, Hammond D. 2016. Patterns of use and perceptions of harm of smokeless tobacco in Navi Mumbai, India and Dhaka, Bangladesh. *Indian Journal of Community Medicine* **41**:280–287 DOI 10.4103/0970-0218.193337.

Nargis N, Hussain AK, Fong GT. 2014. Smokeless tobacco product prices and taxation in Bangladesh: findings from the International Tobacco Control Survey. *Indian Journal of Cancer* **51(Suppl 1)**:S33–S38 DOI 10.4103/0019-509X.151994.

National Cancer Institute and Centers for Disease Control and Prevention. 2014. *Smokeless tobacco and public health: a global perspective.* Bethesda: National Cancer Institute and Centers for Disease Control and Prevention. US Department of Health and Human Services, Centers for Disease Control and Prevention and National Institutes of Health, National Cancer Institute NIH Publication No. 14-7983.

Nemeth J, Liu S, Klein E, Ferketich A, Kwan M, Wewers M. 2012. Factors influencing smokeless tobacco use in rural Ohio Appalachia. *Journal of Community Health* **37**:1208–1217 DOI 10.1007/s10900-012-9556-x.

Perfetti TA, Rodgman A. 2012. *The chemical components of tobacco and tobacco smoke.* Boca Raton: CRC Press.

Renuka P, Pushpanjali K. 2014. Effectiveness of health belief model in motivating for tobacco cessation and to improving knowledge, attitude and behaviour of tobacco users. *Cancer and Oncology Research* **2**:43–50.

Sansone G. 2014. *Acceptability of female smoking and smokeless tobacco use in Bangladesh and India.* Canada: University of Waterloo.

Siddiqi K, Shah S, Abbas SM, Vidyasagaran A, Jawad M, Dogar O, Sheikh A. 2015. Global burden of disease due to smokeless tobacco consumption in adults: analysis of data from 113 countries. *BMC Medicine* **13**:194 DOI 10.1186/s12916-015-0424-2.

Sidhu AK, Sussman S, Tewari A, Bassi S, Arora M. 2016. Project EX-India: a classroom-based tobacco use prevention and cessation intervention program. *Addictive Behaviours* **53**:53–57 DOI 10.1016/j.addbeh.2015.09.005.

Sinha DN, Palipudi KM, Jones CK, Khadka BB, Silva PD, Mumthaz M, Shein NNN, Gyeltshen T, Nahar K, Asma S, Kyaing NN. 2014. Levels and trends of smokeless tobacco use among youth in countries of the World Health Organization South-East Asia Region. *Indian Journal of Cancer* **51(5)**:50–53.

Warren CW, Lea V, Lee J, Jones NR, Asma S, McKenna M. 2009. Change in tobacco use among 13–15-year olds between 1999 and 2008: findings from the Global Youth Tobacco Survey. *Global Health Promotion* **16**:38–90.

World Health Organization (WHO). 1998. World health report 1998: life in the 21st Century, a vision for all. World Health Organization.

World Health Organisation (WHO). 2013. WHO | Bangladesh –National tobacco control law amended. *Available at http://www.who.int/fctc/implementation/news/news_ban/en/* (accessed on 24 May 2018).

World Health Organization (WHO). 2015. Global Youth Tobacco Survey (GYTS), Bangladesh Report, 2013.

World Health Organization (WHO), Regional Office for South-East Asia. 2009. Global adult tobacco survey: Bangladesh report 2009.

National Cancer Research Institute Conference, 2018

Predictors of patient-related delay of oral cancer diagnosis in Bangladesh

Year: 2017

Session type: Proffered paper sessions

Theme: Diagnosis and therapy

Md Zahid Ullah[1], Jennifer NW Lim[2], Marie-Ann Ha[1], Bas Bueno-de-Mesquita[3]

[1]Anglia Ruskin University,[2]University of Wolverhampton,[3]Imperial College London

Abstract

Background

Bangladesh ranked as the second highest country in the world for oral cancer-related death (14.5 per 100,000 populations). Reducing the delay of oral cancer diagnosis can lead to early cancer detection and potentially reduce the mortality rate. Therefore, the aim of this study was to investigate the predictors of patient delay in oral cancer diagnosis among Bangladeshi subjects.

Method

To investigate predictors of patient delay (primary delay) in oral cancer diagnosis, 169 new oral cancer cases were recruited for a hospital-based case-control study. A Multiple Logistic Regression Model was used to estimate the Odds Ratio (OR) with 95% Confidence Interval (CI) of patient delay (more than 90 days from the first onset of sign and symptoms to seeking advice from healthcare professionals).

Results

Out of 169 patients (Mean age: 54 years, Male: 47.9% & female: 52.1%), a total of 59 (35%) patients reported a patient delay of more than 90 days. The mean and median patient delay was 97.5 and 78 days (range 26 -360 days). Using a forward stepwise method for multiple logistic regression analysis, the higher grade of oral cancer (OR=0.34, 95% CI 0.17-0.69, p=0.003) and not visiting the dentist (OR= 5.24, 95% CI 2.57-10.71, p<0.001) were significant predictors of patient-related diagnostic delay.

Conclusion

The findings of this study emphasise the need for an educational and promotional campaign against oral cancer to increase patient awareness. Moreover, patients must be encouraged to visit their dentist regularly in order to increase the early detection rate.

Appendix B-Adolescent cross-sectional survey questionnaire

Instructions:

- This survey is to look at the current prevalence of smokeless tobacco use among 13-15 years old children and their knowledge about the effect on health.
- Please read each question carefully before answering it.
- Choose the answer that best describes what you believe and feel to be correct. We want to know what you think, whatever you believe will be the correct answer.
- On the answer sheet, locate the number that corresponds to your answer and fill it in completely with the pencil that was provided to you.
- If you have to change your answer, do not worry; just erase it completely, without leaving marks.
- Do not put your name on the survey. We do not want to know who answered the questions.
- The answers you give will not be shared with your teacher or your parents. The information will be used by the researcher (Dr Zahid) for his University degree in England.
- If you do not want to fill in the questionnaire, you do not have to.

Introduction:

Thank you for participating in this survey. Before you start, please read the following information that will help you to answer the questions:

- ***Some of the questioBns will ask you about smokeless tobacco, which is tobacco that is not smoked, but is chewed, held in the mouth, or sniffed through the nose. Such as: Zarda, Sadapata, Pan Masala, Gutka, Gul; etc.***

About You

A1. Are you?

- ☐ Male
- ☐ Female

A2. How old are you? __________Years old

A3. What is your father's job if he is working?
____.

A4. What is your mother's job if she is working? ____.

Smokeless tobacco habits

B1. Have you ever used smokeless tobacco, such as Pan with Jarda, Gul, Pan Masala etc, even just a small amount?

- ☐ Yes (If yes, then what brand or type of smokeless tobacco you used ______________________________)
- ☐ No

[If you tried smokeless tobacco, then answer the next questions. Otherwise, go to B15.]

B2. How old were you when you first tried using smokeless tobacco?

- ☐ I have never tried using smokeless tobacco
- ☐ 7 years old or younger
- ☐ 8 or 9 years old
- ☐ 10 or 11 years old
- ☐ 12 or 13 years old
- ☐ 14 or 15 years old

B3. During the past 30 days, on how many days did you use smokeless tobacco?

- ☐ 0 days
- ☐ 1 or 2 days
- ☐ 3 to 5 days
- ☐ 6 to 9 days
- ☐ 10 to 19 days
- ☐ 20 to 29 days
- ☐ All 30 days

B4. How many times did you usually use smokeless tobacco per day, in past 30 days?

- ☐ I did not use smokeless tobacco during the past 30 days
- ☐ Less than once per day
- ☐ Once per day
- ☐ 2 to 5 times per day
- ☐ 6 to 10 times per day
- ☐ 11 to 20 times per day

- ☐ More than 20 times per day

B5. Do you ever use smokeless tobacco or feel like using smokeless tobacco first thing in the morning?

- ☐ No, I do not use or feel like using smokeless tobacco first thing in the morning
- ☐ Yes, I sometimes use or feel like using smokeless tobacco first thing in the morning
- ☐ Yes, I always use or feel like using smokeless tobacco first thing in the morning.

B6. How soon after you use smokeless tobacco, do you start to feel a strong desire to use it again that is hard to ignore?

- ☐ I never feel a strong desire to use it again after using smokeless tobacco
- ☐ Within 60 minutes
- ☐ 1 to 2 hours
- ☐ More than 2 hours to 4 hours
- ☐ More than 4 hours but less than one full day
- ☐ 1 to 3 days
- ☐ 4 days or more.

B7. Why do you use smokeless tobacco?

- ☐ Taste
- ☐ Smell
- ☐ Pleasure
- ☐ To feel better/good/Happy
- ☐ Because my friend is using it
- ☐ Do not Know
- ☐ Other reason (Please Specify) _ ______________________________

B8. Do you want to stop using smokeless tobacco now?

- ☐ I do not use smokeless tobacco now
- ☐ Yes
- ☐ No

B9. During the past 12 months, did you ever try to stop using smokeless tobacco?

- ☐ I did not use smokeless tobacco during the past 12 months
- ☐ I tried, but not successful
- ☐ No

B10. **If you have tried to stop, but not successful, Why?**
____.

B11. Have you ever received help or advice to help you stop using smokeless tobacco?

- ☐ Yes, from a programme or professional
- ☐ Yes, from a friend
- ☐ Yes, from a family member
- ☐ No

B12. The last time you used smokeless tobacco during the past 30 days, how did you get it? (If necessary, you can give more than one answer)

- ☐ I did not use smokeless tobacco during the past 30 days
- ☐ I bought it in a store or shop in the school canteen
- ☐ I bought it from a street vendor outside the school gate
- ☐ I got it from someone else
- ☐ I bought it from a store near to my house
- ☐ i bought it from a store on the way to school
- ☐ I got it some other way.- if you are willing to state how, please do - __________________________________

B13. During the past 30 days, did anyone refuse to sell you smokeless tobacco because of your age?

- ☐ I did not try to buy smokeless tobacco during the past 30 days
- ☐ Yes, someone refused to sell me smokeless tobacco because of my age
- ☐ No, my age did not keep me from buying smokeless tobacco

B14. During the past 30 days, did you see any health warnings on smokeless tobacco packages?

- ☐ Yes, but I did not think much of them
- ☐ Yes, and they led me to think about quitting smokeless tobacco or not starting smokeless tobacco
- ☐ No

B15. If one of your best friends offered you smokeless tobacco, would you use it?

- ☐ Definitely not
- ☐ Probably not
- ☐ Probably yes

- ☐ Definitely yes

B16. Once someone has started using smokeless tobacco, do you think it would be difficult for them to quit?

- ☐ Definitely not
- ☐ Probably not
- ☐ Probably yes
- ☐ Definitely yes

Health effects of Smokeless tobacco

C1. Do you think smokeless tobacco use is:

- ☐ Good for your health
- ☐ Neither good nor bad for your health
- ☐ Not good for your health
- ☐ Do not Know

C2. Are there benefits of smokeless tobacco to your body and health?

- ☐ Yes
- ☐ No

C3. Does smokeless tobacco cause less harm to your health compare to smoking tobacco?

- ☐ Yes
- ☐ No
- ☐ Do not Know

C4. Does smokeless tobacco cause white patches in the mouth?

- ☐ Yes
- ☐ No
- ☐ Do not Know

C5. Can smokeless tobacco cause oral cancer?

- ☐ Yes
- ☐ No
- ☐ Do not Know

C6. Does smokeless tobacco cause Gum diseases (*Gum disease is an infection of the gum that surround and support your teeth*)?

☐ Yes
☐ No
☐ Do not Know

C7. Does smokeless tobacco cause heart disease?

☐ Yes
☐ No
☐ Do not Know

C8. Does smokeless tobacco contain nicotine? ***(Nicotine is a chemical that is present in cigarettes that makes people become addicted)?***

☐ Yes
☐ No
☐ Do not Know

Appendix C- Approval from school headteachers

Dr Md Zahid Ullah
PhD student
Anglia Ruskin University
Cambridge
CB1 1PT
United Kingdom

Date: 25.08.15

Dear Zahid,

Re: PhD study on "The risk and prevalence of Leukoplakia and Oral Cancer of smokeless tobacco use in Bangladesh" (Dr Md Zahid Ullah, ID: 1360111).

Thank you for your letter dated 24th August 2015, in which you requested for support from our school to assist you in conducting survey among 13-15 years old students.

We are very happy to be able to assist and support you in this survey in any way possible to ensure the success of your research.

Thank you

Regards

Permitted

[redacted]

Dr Md Zahid Ullah
PhD student
Anglia Ruskin University
Cambridge
CB1 1PT
United Kingdom

Date: 28·08·2015

Dear Zahid,

Re: PhD study on "The risk and prevalence of Leukoplakia and Oral Cancer of smokeless tobacco use in Bangladesh" (Dr Md Zahid Ullah, ID: 1360111).

Thank you for your letter dated 24th August 2015, in which you requested for support from our school to assist you in conducting survey among 13-15 years old students.

We are very happy to be able to assist and support you in this survey in any way possible to ensure the success of your research.

Thank you

Regards

[redacted]

Appendix D- Parent consent form

Your child is invited to taking part in the school-based Survey organised by Allied and Public Health Department of Anglia Ruskin University, United Kingdom and your child school. The survey will ask about Smokeless tobacco use and their knowledge about its' harmful effects of 7th to 9th-grade students.

Students will be asked to fill out a questionnaire that takes about 15 minutes to complete.

Doing this paper and pencil survey will cause little or no risk to your child. The only potential risk is that some students might find certain questions to be sensitive. The survey has been designed to protect your child's privacy. Students will not put their names on the survey. Also, no school or student will ever be mentioned by name in a report of the results. Your child will get no benefit right away from taking part in the survey. However, the results of this survey will help children in the future. We would like all selected students to take part in the survey, **but the survey is voluntary**. **No** action will be taken against the school, you, or your child, if your child does not take part. Students can skip any question that they do not wish to answer. In addition, students may stop participating in the survey at any point without penalty.

Please read the section below. If you do not want your child to take part in the survey, please check the box and return the form to the school no later than [16.09.2015]. Please see the other side of this form for more facts about the survey. If your child's teacher or principal cannot answer your questions about the survey, contact:

Dr Md Zahid Ullah MBA, MPH, BDS
Doctoral Student, Anglia Ruskin University
East Road, Cambridge Campus, CB1 1PT.
United Kingdom.
Email: [e-mail address redacted]
Phone: [number redacted]
Thank you.

____

Child's name: ____ Grade: _____________

I have read this form and know what the survey is about.

[] My child may not take part in this survey.

Parent's signature: ______________________________________
Date:________________

Phone number: ____

PARTICIPANT INFORMATION SHEET

Section A: The research project:

Title: "The risk and prevalence of Oral Cancer and Oral Leukoplakia of Smokeless tobacco use in Bangladesh."

Study Purpose: Recent Research had shown adolescents from the South-Asian region are more likely to be smokeless tobacco users. Studies from neighbour countries like India and Pakistan had shown higher numbers of adolescent (13-18 years old) smokeless tobacco users. In this scenario, it is essential to explore the current prevalence of smokeless tobacco use and knowledge about its harmful effect among Bangladeshi adolescents (13-18). So, the aim of this study is to explore the current prevalence of smokeless tobacco use and knowledge about its harmful effect namely Oral Cancer and Oral Leukoplakia. The result of the study will help Bangladesh Government to come up with a better educational campaign for the adolescents and may reduce the burden of smokeless tobacco use and its harmful effect in future.

"Smokeless tobacco is tobacco or a tobacco product that is used by means other than smoking. These uses include chewing, sniffing, placing the product between the teeth and gum. Such as Pan with Zarda, Sadapata, Pan Masala, Gutka etc."

"Oral Leukoplakia is a white or grey patch that develops on the tongue, the inside of the cheek, or on the floor of the mouth. It is the mouth's reaction to chronic irritation of the mucous membranes of the mouth."

"Oral cancer is also known as mouth cancer, is where a tumour develops on the surface of the tongue, mouth, lips or gums."

Invitation: Your child is invited to take part in this survey in their school. Their participation will help us to explore the current prevalence of smokeless tobacco use and knowledge about its harmful effect among adolescents in Bangladesh**.**

Who is organising the study?

The study is organised by The Department of Allied and Public Health, Faculty of Medical Science, Anglia Ruskin University, United Kingdom and School Name ______________________________.

What will happen to the result of the study?

The result of the study will be published in the scientific journals and articles.

Contact Information:

Dr Md Zahid Ullah MBA, MPH, BDS
Doctoral Student, Anglia Ruskin University
East Road, Cambridge Campus, CB1 1PT.
United Kingdom.
Email: [e-mail address redacted]
Phone Number: [number redacted]

Section B: Your child's Participation in the research project

Why your child has been invited to take part?

The aim of the survey is to explore the prevalence of smokeless tobacco use and knowledge about its harmful effect among 13 to 18 years old adolescents. According to the school record, your child is eligible to take part in this survey.

Whether you can refuse to give consent for your child to take part?

Participation in this research project is entirely voluntary. You are absolutely free to refuse to give consent for your child to take part in this study.

Whether your child can withdraw at any time, and how?

Your child is free to withdraw from this study at any time – even in the middle of the survey.

What will happen if you agree for your child to take part?

If you agreed for your child to take part in this study, we would ask your child to attain a survey in their school either with the researcher. The survey will not take more than 15 minutes. The questionnaires will have three different sections. In the first section, we will ask about their age, father's and mothers' educational background and their professions. In the second section there will be questions about the smokeless tobacco habits, the third section there will be questions about the harmful effect of smokeless tobacco use.

Whether there are any risks involved (e.g. side effects from taking part) and if so what will be done to ensure your wellbeing/safety?

There is no major risk involved from taking part in this study. Your child's name will not be used in anywhere, so it will be impossible to identify that who had provided the information.

Does agreement to participate in this research, compromise your child's legal rights, should something go wrong?

Agreement to participate in this research will not compromise your child's legal rights if something goes wrong.

Whether there are any special precautions, your child must take before, during or after taking part in the study?

You do not need to take any special precautions before, during or after taking part in the study. There is no risk associated with participating in this study; It involves only the collection of data by means of a survey.

What will happen to any information/data/samples that are collected from your child?

Any information/ data that are collected from your child will be published in Academic journals, articles and research seminars.

Whether there are any benefits from taking part?

Participants will not benefit directly from their participation in this study. However, the results from this study may help the Bangladesh Government to come up with the effective educational campaign.

How your child's participation in the project will be kept confidential?

We assure that all information gathered during the course of this research project will be kept entirely confidential. Only the researchers involved in this project and the research assistants gathering the data will have access to the information you child provided, which will be kept locked in the research office. All the data will be identified by a code number, so we will not know to whom the data are related. The results of the research will be published in scientific journals in an anonymous form. All the data will be kept for a period of 5 years, after which they will be destroyed.

Appendix E- Knowledge score allocation

Name of the Item	Allocated Score
Do you think smokeless tobacco use is?	Good for your health (Score 0) Neither good nor bad for your health (Score 0) Not good for your health (Score 1) Do not Know (Score 0)
Are there benefits of smokeless tobacco to your body and health?	Yes (Score 0) No (Score 1)
Does smokeless tobacco cause less harm to your health compared to smoking tobacco?	Yes (Score 0) No (Score 1) Do not Know (Score 0)
Does smokeless tobacco cause white patches in the mouth?	Yes (Score 0) No (Score 1) Do not Know (Score 0)
Can smokeless tobacco cause oral cancer?	Yes (Score 0) No (Score 1) Do not Know (Score 0)
Does smokeless tobacco cause Gum diseases?	Yes (Score 0) No (Score 1) Do not Know (Score 0)
Does smokeless tobacco cause heart disease?	Yes (Score 0) No (Score 1) Do not Know (Score 0)
Does smokeless tobacco contain nicotine?	Yes (Score 0) No (Score 1) Do not Know (Score 0)

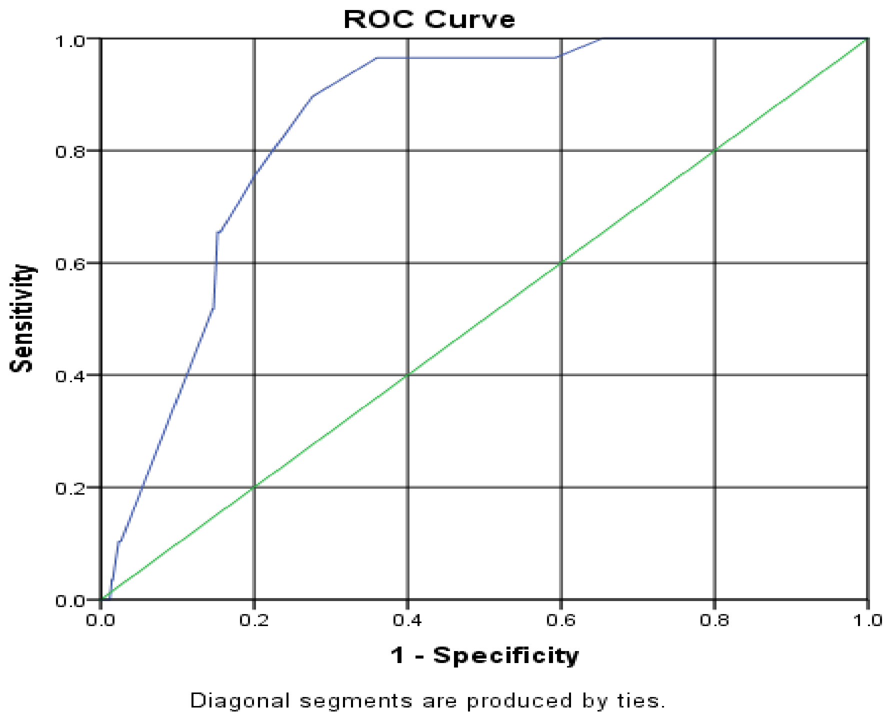
Appendix F- Model diagnostics

Multivariate model diagnostics:

Model diagnosis

df	Likelihood Chi-square	Likelihood P-value	Model Accuracy
6	41.4	2×10^{-7}	82%

Table 36 shows that the likelihood test result was statistically significant which indicates that the final model fits the data better than the Null model (model with no predictors) where the *p*-value for the likelihood ratio test was less than 0.05. The model correctly classified 82% of the dependent variable which is considered fairly accurate.



As mentioned above, the model correctly classified 82% of the data. The ROC curve shows that the AUC is 84.69% which indicates a good predictive power (>0.8). As a rule of thumb, a model with good predictive ability should have an AUC closer to 1 (1 is ideal) than to 0.5 (Hosmer *et al.*, 2013).

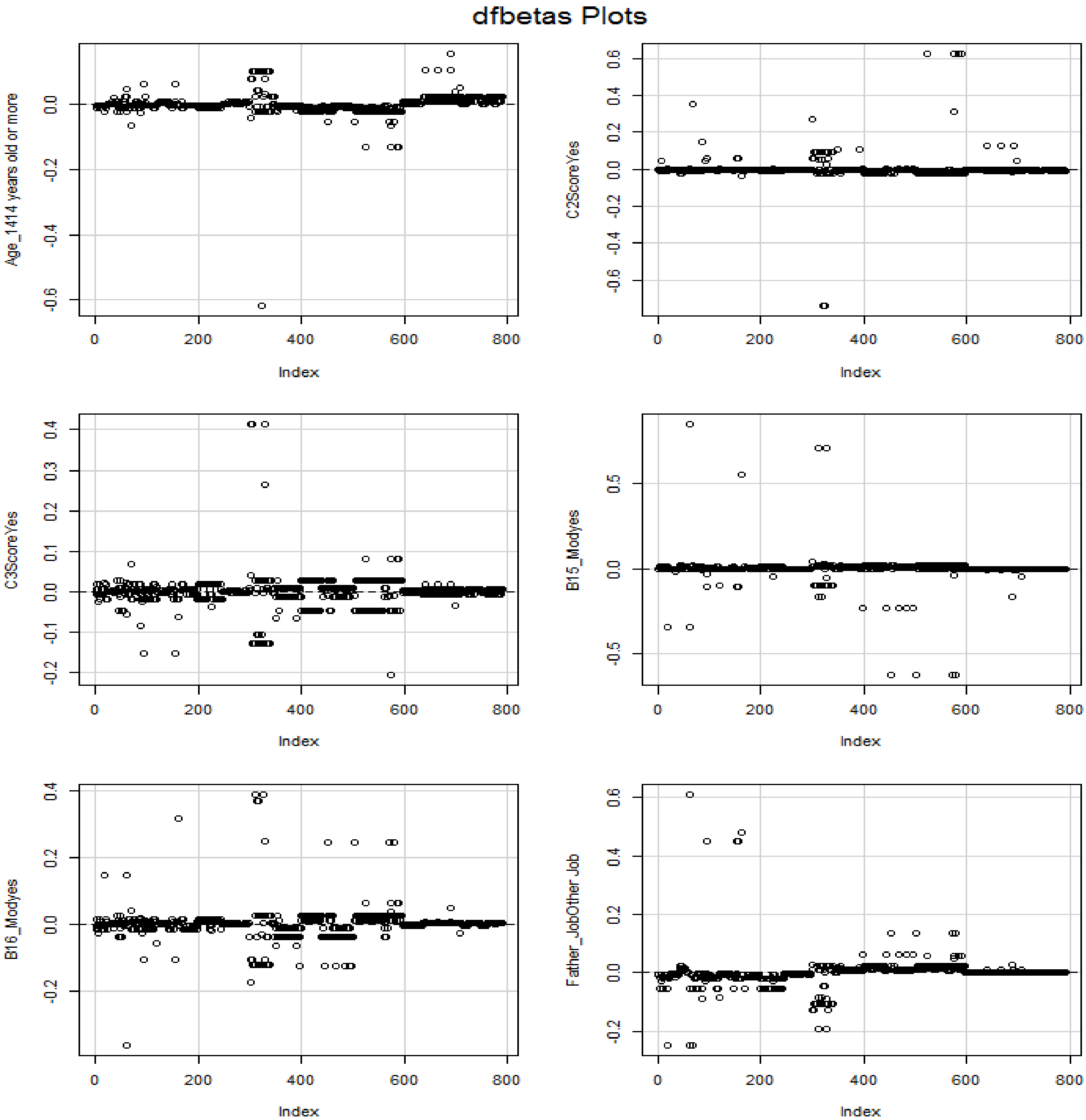
AUC (Area Under Curve) test of the final predictive model

Test Result Variable(s): Predicted probability

			Asymptotic 95% Confidence Interval	
Area	Std. Error[a]	Asymptotic Sig.[b]	Lower Bound	Upper Bound
.847	.025	.000	.799	.895

a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

Deviance residuals also indicate that the model was a good fit for the data where the coefficients did not change significantly with the removal of any of the data points



dfbetas Plots
Age_1414 years old or more
C2ScoreYes
C3ScoreYes
B15_Modyes
B16_Modyes
Father_JobOther_Job
Index

Appendix G- Hospital-based case-control study questionnaire

Section A. Medical information

Interviewer Reminder: Prior to interview, obtain the information below from hospital medical records

Identification number:.. ☐☐☐☐

A1 Status.. ☐☐

(01)Case (02) Control

FOR CONTROL:

A2. Control Department: (*Code 88 For cases).*... ☐☐

(01)Dental department (04) Out Patient Department (OPD)
(02)Surgery
(03)Medicine

A3. Main Diagnosis of control____ ☐☐

FOR CASES:

A4. Type of cases?.. ☐☐

(01)Oral cancer (Go to Q. A7) (02) Oral Leukoplakia.

A5 Oral Leukoplakia Site.. ☐☐

(01)Gums (04) Right Cheek (07) Middle of the tongue (10) Floor of the mouth
(02)Lower Lip (05) Right side of the Tongue (08) Back of the tongue (11) Soft Palate
(03)Left Cheek (06) Left Side of the Tongue (09) Under surface of the tongue.
(12) Oral Leukoplakia with Overlapping Region.

A6. Extent of the Oral Leukoplakia.. ☐☐Mm.

A7. Cancer Site:.. ☐☐

(01)Gums (04) Right Cheek (07) Middle of the tongue (10) Floor of the mouth
(02)Lower Lip (05) Right side of the Tongue (08) Back of the tongue (11) Soft Palate
(03)Left Cheek (06) Left Side of the Tongue (09) Under surface of the tongue
(12) Oral Cancer with Overlapping Region

For All the Subjects:

A8. Date of Diagnosis........................ ☐☐Month☐☐99-9999☐☐☐☐

A9. Time since Diagnosis (Days)..

A10. Time since Pre-Diagnostic complaints, sign and symptoms Days/Months..

A11. Interviewer's name:...

A12. Date of Medical Data collection... onth

Section B. General Information

B1. Date of interview.................................... Mont

B2. Time of beginning of the interview....... Hour Min

B3. Sex..

(01)Male (02) Female

B4. How old are you?.................................. Old

B5. What is your marital status?.................

(01)Single (02) Married (03) Divorced

B6. What is the highest level of education you have completed?..

(01) No-formal education (05) High School completed (09) Refused
(02) Less than primary school completed (06) College, University completed
(03) Primary school completed (07) Postgraduate degree completed
(04) Less than high school completed (08) Don't know.

B7. Which of the following best describes your main work status last 12 months?................................

(01) Government Employee (07) Daily labourer (13) Unemployed, unable to work
(02) Non-Government employee (08) Other Self employed (14) Other, Please specify________
(03) Business small (09) Student
(04) Business Large (10) House worker
(05) Farming (11) Retired
(06) Industrial workers (12) Unemployed, able to work

B8. Weight measurement?.......................... Lbs

B 9. Height Measurement?......................... Feet In

Section C. Smokeless tobacco habits

Interviewer Reminder: Use the life grid if necessary to help answer Q C1 to C4.
- ***Avoid overlapping years for the same product, type of cigarette or amount smoked, i.e. Record 30-40, 41-45 rather than 30-40, 40-45.***
- ***Only note changes occurring in one year or more.***
- ***Exclude quitting during pregnancy(ies) if for less than one year.***

C1. Do/ did you use chewing tobacco, betel quid, Areca nut and/or pan masalla etc? ☐☐

(00) Never (Go to C4) (01) Yes, I still do (02) Yes, only in the past

From age To age (A) Type (B) Duration Consumption Per
(Minutes) (How many) (C)

☐☐	☐☐	☐☐	☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐	☐☐	☐☐

To age (A)	**Type (B)**	**Per (C)**
If still taking smokeless tobacco products, write age of the time of interview	(01)Zarda only (02)Betel quid with Zarda (03)Betel quid without Zarda (04)Areca nut with Zarda (05)Areca nut without Zarda (06)Sadapata only (07)Betel quid with Sadapata (08)Gul (09)Pan masala (10)Betel leaf (11)Other, specify___________	(01)Day (02)Week (03)Month

C2. When you chew tobacco, where in your mouth you usually keep it, on the left side or the right side? ☐☐

(01) Left (02) Right (03) Both.

C3. Did you ever use snuff?..

(00)No (Go to section D) (01) yes (02) yes, only in the past

From Age To age (A) Consumption Per (C)
(How many)

To Age (A) If still using, write age at the time of interview	Per (C) (01)Day (02)Week (03)Month

C4. Which brand of snuff you use most often? _______________

C5.When using snuff Do you usually take it by nose or mouth?..

(01)Nose (Go to next Section) (02) Mouth (03) both.

C6. How long do you keep snuff in your mouth? __________ Minutes

C7. When you take snuff, where in your mouth you usually keep it, on the left side or the right side?.......

(01) Left (02) Right (03) Both.

C8. Do you usually place the snuff towards the front or the back of the mouth?...

(01) The front (02) The back (03) The centre.

Section D. Smoking Habits

D1. Have you ever smoked in your life?...

(00)Never (Go to next section) (01) Occasionally (02) Yes (I still do) (03) Yes, but only in the past.

D2. Did you ever Smoke cigarettes?...

(00 No (Go to next Q, D3) (01) Yes (02) Yes, only in the past.

From Age To age (A) Type (B) Consumption Per
(How Many) (C)

To age (A) If still smoking, write age of the time of interview	Type (B) (01) Filter (02)Non-Filter (03)Hand-Rolled	Per (C) (01) Day (02)Week (03)Month

D3. Did you ever smoke bidis?...

(00) No (Go to section.D 4) (01) Yes (02) Yes, only in the past

From Age To age (A) Consumption Per (C)
(How many)

To Age (A) If still using, write age at the time of interview	Per (C) (01) Day (02) Week (03) Month

D4. Did you ever smoke, water pipe/ Hukkah?...

(00) No (Go to Q.D5) (01) Yes (02) Yes, only in the past

From Age To age (A) Consumption Per (C)
(How many pipes full of tobacco)

To Age (A) If still using, write age at the time of interview	Per (C) (01) Day (02) Week (03) Month

D5. Did/Do you smoke cigar?.. ☐☐

(00) No (Go to next section) (01) Yes (02) Yes, only in the past

From Age To age (A) Consumption Per (C)
(How many)

To Age (A) If still using, write age at the time of interview	Per (C) (01) Day (02) Week (03) Month

Section E. Drinking Habits

E1. Did you ever drink alcoholic beverages at least once a month ☐☐

(00) No (Go to next section) (01) Yes, I do (02) Yes Only in the past

E2. When Do/ did you usually drink alcoholic beverages?.............

(01)With meals (03) Both
(02)Between meals (04) Only at social events.

E3. Beverages if (A) – (05) From Age To Age Unit Consumption Per
(A) Then Specify (B) (How Many) (C)
Other beverages

Beverages (A)	Unit (B)	Per (C)
(01)Local Toddy (02)Wine (03)Bear (04)Hard liquor (>35) (whisky, vodka, brandy, rum,gin) (05)Other, Specify......................................	(01)Small glass (50ml) (1-2oz) (02)Medium glass (100ml) (2-3oz) (03)Big glass (250ml) (1/2 pint) (04)½ small bottle (330ml) (1beer) (05)Bottle (700-750ml) 921oz)	(01)Day (02)Week (03)Month

Section F. Oral Health

I am going to ask you some questions about your oral health before your diagnosis/ being seen at this clinic and at a different time in your lifetime.

F1. Did you wear complete dentures?..

(00) No (Go to question F4) (02) yes, top only

(01) Yes bottom only (go to question F3) (03) yes, top and bottom.

F2. At what age did you start wearing complete top dentures? Years.......................................

F3. At what age did you start wearing complete bottom dentures? Years.............

(Code 888 if F1 = 02)

F4. Did you wear partial dentures?...

(00)No (02) yes, bottom only
(01)Yes, top only (03) yes top and bottom.

F5. What instrument you use to clean your teeth?..

(01) Toothbrush (02) Fingers (03) Sticks (04) Others, specify_________________.

F6. How often do you clean your teeth?...

(00)Never (03) Every other day
(01)Less than once a week (04) Once a day
(02)1-2 times a week (05) twice or more a day.

F7. Did you use any kind of substance to clean your teeth?..

(00)No
(01) Charcoal
(02)Toothpaste
(03)Tooth Powder
(04)Other, specify_____________________.

F8. Did your gums bleed, when you clean your teeth?..

(00)No (01) Sometimes (02) Always or almost always.

F9. Have you ever had an ulcer or a cut because of denture or a tooth?................................

(00)No (01) Yes.

F10. In the last 20 years how often did you see a dentist?...

(00)Never (03) Every 2-5 Years
(01)Every 6 Months (04) Once every 5 years
(02)Every year (05) Only when I had Pain.

G1. Has any member of your biological family ever had cancer?.................................. ..

(00)No (01) Yes (99) Don't know.

G2. Relationship status Current/ last age Type of Cancer Age at Diagnosis
(A) (B) (C) (D)

Relationship (A)	Status (B)	Current/ Last age (C)	Age of Diagnosis (D)
(01)Mother (02)Father (03)Sister (04)Brother (05)Daughter (06)Son (07)Grand mother (08)Grand Father (09)Aunty/Uncle	(01)Deceased (02)Alive	(999) Don't know If alive write the current age. If deceased, give age at death	(999) Don't know

.

Appendix H -Life Grid

Other events	Residence	Year	Age	Education/jobs	Habits
			5		
			10		
			15		
			20		
			25		
			30		
			35		
			40		
			45		
			50		
			60		
			70		

Appendix I- Ethical Approval

Anglia Ruskin University

Cambridge Chelmsford Peterborough

Chelmsford Campus
Bishop Hall Lane
Chelmsford
CM1 1SQ

T: 0845 196 4779
Int: +44 (0)1245 493131
www.anglia.ac.uk

Ref: NS/jc/FMSFREP/15-039
Enquiries: [redacted]
Direct Line:
Date: 15th June 2015

Mohammad Zahid Ullah

Dear Mohammad

Re: Application for Ethical Approval

Principal Investigator:	Mohammad Zahid Ullah
FREP number:	15/039
Project Title:	Risk and Prevalence of Oral Cancer and Oral Leukoplakia of Smokeless tobacco use in Bangladesh.

Thank you for your application for ethical approval which has now been considered by the Faculty (of Medical Science) Research Ethics Panel (FREP).

I am pleased to inform you that your application has been approved by the Faculty Research Ethics Panel Chair under the terms of Anglia Ruskin University's Research Ethics Policy (Dated 23/6/14, Version 1). Ethical approval is given for 3 years from the date of this letter.

It is your responsibility to ensure that you comply with Anglia Ruskin University's Research Ethics Policy and the Code of Practice for Applying for Ethical Approval at Anglia Ruskin University, including the following.

- The procedure for submitting substantial amendments to the committee, should there be any changes to your research. You cannot implement these changes until you have received approval from FREP for them.
- The procedure for reporting adverse events and incidents.
- The Data Protection Act (1998) and any other legislation relevant to your research. You must also ensure that you are aware of any emerging legislation relating to your research and make any changes to your study (which you will need to obtain ethical approval for) to comply with this.
- Obtaining any further ethical approval required from the organisation or country (if not carrying out research in the UK) where you will be carrying the research out. Please ensure that you send the FREP copies of this documentation if required, prior to starting your research.

- Any laws of the country where you are carrying the research and obtaining any other approvals or permissions that are required.
- Any professional codes of conduct relating to research or research or requirements from your funding body (please note that for externally funded research, a Project Risk Assessment must have been carried out prior to starting the research).
- Notifying the FREP Secretary when your study has ended.

Please also note that your research may be subject to random monitoring.

Should you have any queries, please do not hesitate to contact my office. May I wish you the best of luck with your research.

Yours sincerely,

[redacted]

Dr Nigel Sansom
Director of Research
For the Faculty (of Medical Science) Research Ethics Panel

Letter from dental college redacted due to confidentiality considerations.

Appendix J- Patient Consent form

Anglia Ruskin University

Cambridge Chelmsford Peterborough

Patient Consent Form

Name of the Participant:

Title of the project:

"The Risk and Prevalence of Oral Leukoplakia and Oral Cancer of Smokeless Tobacco Use in Bangladesh".

Main Investigator and Contact Details:

Dr Md Zahid Ullah MBA, MPH, BDS
Doctoral Student, Anglia Ruskin University
East Road , Cambridge Campus, CB1 1PT .
United Kingdom.
Email: [redacted]
Phone Number: [redacted]

Member of the research team: ______________________.

1. I agree to take part in the above research. I have read the Participant Information Sheet for the study. I understand what my role will be in this research, and all my questions have been answered to my satisfaction.
2. I understand that I am free to withdraw from the research at any time, for any reason and without prejudice.
3. I have been informed that the confidentiality of the information I provide will be safeguarded.
4. I am free to ask any questions at any time before and during the study.
5. I will not have waived any of my legal rights by signing this consent form.
6. I have been provided with a copy of this form and the Participant Information Sheet.

Name of participant (print)..............................Signed.......................Date..................

YOU WILL BE GIVEN A COPY OF THIS FORM TO KEEP

If you wish to withdraw from the research, please complete the form below and return to the main investigator named above.

Title of Project

I WISH TO WITHDRAW FROM THIS STUDY

Signed: ______________________ Date: ______________

Appendix K- Post-hoc power calculation of case-control study

A post-hoc power calculation was conducted from the preliminary findings of the study, where 71% of cases and 26.6% of controls were SLT users. With a two-sided confidence interval of 95% and 5% type I error, the study attained 100% power. See the calculation below (Levine and Ensom, 2001):

$$Power = \Phi\left\{\frac{\Delta}{\sqrt{p_1q_1/n_1 + p_2q_2/n_2}} - z_{1-\alpha/2} * \frac{\sqrt{\bar{p}\bar{q}(1/n_1+1/n_2)}}{\sqrt{p_1q_1/n_1+p_2q_2/n_2}}\right\}$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + kp_2}{1+K}$$

$$\bar{q} = 1 - \bar{p}$$

$$Power = \Phi\left\{\frac{0.444}{\sqrt{0.71*0.29/169+0.266*0.734/338}} - 1.96 * \frac{\sqrt{0.414*0.586(1/169+1/338)}}{\sqrt{0.71*0.29/169+0.266*0.734/338}}\right\}$$

$$Power = \Phi(8.331) = 1 = 100\%\ power$$

p1, p2 = proportion (incidence) of cases and controls
Δ = |p2-p1| = absolute difference between two proportions
n1 = sample size of cases
n2 = sample size of controls
α = probability of type I error (0.05)
z = critical Z value for a given α or β
K = ratio of sample size for controls to cases
Φ() = function converting a critical Z value to power

Appendix L- School survey instrument student evaluation review

Please circle your response to the following questions.

1. Did you understand the directions on how to complete this questionnaire?

Yes No

2. Did the title clearly tell you what the questionnaire was about?

Yes No Unsure

3. Were there any questions that you were unable to answer completely or correctly because the question was not asked clearly?

Yes No Unsure

4. Were there any questions that you were unable to answer because they were too personal?

Yes No

5. Were there any multiple-choice questions that did not provide a complete list of choices?

Yes No

6. Do you think the questionnaire was too long?

Yes No

7. Were there any words in the questionnaire that you did not know the meaning?

Yes No Unsure

8. Were you provided with clear directions as to what to do with the questionnaire when finished?

Yes No

9. Do you believe that if you were to be in this study your responses would be kept confidential?

Yes No Unsure

10. Were the purposes o f the study clearly explained to you?

Yes No

11. Were you given the name, address, and phone number o f the person conducting the study in case you want to ask questions?

Yes No